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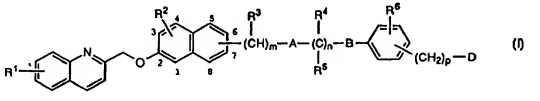

(I)

(57) Abstract

The present invention relates to novel naphthalene quinolines of formula (I), wherein the substituent containing A is bound to the 6- or 7-position of the 2-naphthol system; -R^1, R^2, R^6 are independently hydrogen, fluorine, chlorine, bromine, -OCH_3 or (C_1-C_4)-alkyl; R^3 is hydrogen or methyl; R^4, R^5 are independently hydrogen, -OH, -NH_2, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylamino, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonylamino, (C_1-C_4)-alkoxycarbonylalkyl, carbamoyl, carbamoylalkyl, N,N-dialkylcarbamoylalkyl; -A- is a diradical -O-, -S-, -SO_2-, -SO-, -SO_2NR^7- or -NR^7SO_2- wherein R^7 is hydrogen or (C_1-C_4)-alkyl; B is a sulfur or oxygen atom or a -SO_2- or -SO- group or a single bond; D is a 5-tetrazolyl or -$COOR^8$ group, wherein R^8 is hydrogen, a (C_1-C_4)-alkyl; or a phenylalkyl group of less than 10 carbon atoms; m is an integer from 0 to 4; n and p are integers from 0 to 6, with the proviso that n + p is less or equal to 6. Said compounds show a leukotriene-antagonistic activity, and they are valuable as anti-inflammatory and antiallergic medicaments or in the treatment of cardiovascular diseases.

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NAPHTHALENE QUINOLINES HAVING LEUKOTRIENE-ANTAGONISTIC ACTION

The present invention relates to novel naphthalene quinolines, the pharmaceutically acceptable salts and solvates thereof and pharmaceutical compositions containing them, having a leukotriene-antagonistic activity. The present invention also relates to a process for the preparation of the novel naphthalene quinolines, as well as to the therapeutic use thereof.

TECHNOLOGICAL BACKGROUND

It is well known that most eicosanoids, prostaglandins, leukotrienes and related compounds derive from a fatty acid having 20 carbons and 4 unsaturations, called arachidonic acid (AA), which fundamentally esterifies the hydroxyl at the 2- position of the glycerol of the phospholipids contained in the cell membranes. AA is released from the phospholipid containing it by the action of a lipase, phospholipase A_2 (PLA_2) ("CRC Handbook of Eicosanoids and Related Lipids", vol. II, Ed. A.L.Willis, CRS Press Inc., Florida (1989)). After being released AA is metabolized in mammals mainly by two different pathways or enzyme systems. Through cyclooxygenase it produces prostaglandins and thromboxanes, the most significant being PGE_2 and TxA_2, which are directly involved in inflammation (Higgs et al. Annals of Clinical Research, 16, 287 (1984)). Through lipoxygenase it produces leukotrienes, the most important being LTB_4, and the peptide-leukotrienes LTC_4, LTD_4 and LTE_4. All of them are also involved in inflammatory reactions, exhibiting

chemotactic activities, stimulating the secretion of lysosomic enzymes and playing an important role in immediate hypersensitivity reactions (Bailey and Casey, Ann. Rep. Med. Chem., 17, 203 (1982)). Leukotriene LTB_4 is a strong chemotactic agent which promotes the infiltration of leukocytes and their subsequent degranulation. (Salmon et al., Prog. Drug Res., 37, 9 (1991)). It has been widely shown that LTC_4 and LTD_4 have strong constrictive action on human bronchi (Dahlen et al., Nature, 288, 484 (1980)), causing the obstruction of airways by inflammation and mucus production (Marom et al., Am. Rev. Resp. Dis., 126, 449 (1982)), being thus involved in the pathogenesis of bronchial asthma, chronic bronchitis, allergic rhinitis, etc. Peptide-leukotrienes also bring about a blood extravasation caused by the increase of vascular permeability (Camp et al., Br. J. Pharmacol., 80, 497 (1883)) and are involved in some inflammatory diseases such as atopic eczema and psoriasis. On the other hand, several effects of peptide-leukotrienes on human cardiovascular system have been observed; they are mainly involved in the pathogenesis of the ischaemic cardiopathy. This relationship has been confirmed by the fact that coronary arteries can produce these mediators (Piomelli et al., J. Clin. Res., 33, 521A (1985)). These effects, together with the strong contractions observed in heart tissue caused by LTC_4 and LTD_4, suggest that these mediators might contribute to other cardiovascular disorders, such as coronary spasm, heart anaphylaxis, cerebral oedema and endotoxic shock.

From what said above it follows that the control of

the biological activity of leukotrienes through compounds which inhibit their release or antagonize their effects, represents a new rational approach to the prevention, elimination or improvement of different allergic, anaphylactic, inflammatory and thrombotic conditions, in which such mediators are involved.

In literature some compounds have been described that can be considered as structurally related to the compounds of the present invention, having an inhibitory action on enzyme 5-lipoxygenase, and a leukotriene antagonistic activity. Mauleón D. et al. (Spanish Patent Application ES 9401696/8) disclosed a series of naphthalene amides as leukotriene antagonists. All of the compounds disclosed in the cited patent application have an amide group as the most characteristic functional group in their structure, the compounds disclosed in the present invention being not included within their general formula.

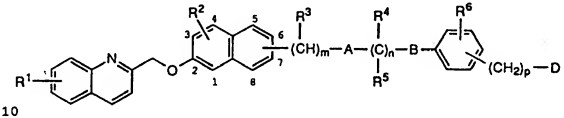
On the other hand, Huang F. C. et al. (US 4920131, EP 315399, US 4920131, and EP 348155) disclosed quinoline ethers, thioethers, sulfoxides, solfones, amides, ketones and amines with an inhibitory action on 5-lipoxygenase and a leukotriene antagonistic activity. Said compounds generally have in their general formulae only phenyl quinolines, the naphthalene quinolines of the present invention being therefore definitely excluded.

The obtention of compounds with high leukotriene antagonistic activity and good oral bioavailability is still a problem in the therapy. The present invention provides a number of novel compounds that exhibit the

above mentioned antagonistic action and that are useful in therapy.

DISCLOSURE OF THE INVENTION

The present invention provides novel naphthalene quinolines of general formula I,



I

wherein:

the substituent containing A is bound to the 6- or 7-position of the 2-naphthol system;

$-R^1$, R^2, R^6 are independently hydrogen, fluorine, chlorine, bromine, $-OCH_3$ or (C_1-C_4)-alkyl;

$-R^3$ is hydrogen or methyl;

$-R^4$, R^5 are independently hydrogen, $-OH$, $-NH_2$, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylamino, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonylamino, (C_1-C_4)-alkoxycarbonylalkyl, carbamoyl, carbamoylalkyl, N,N-dialkylcarbamoylalkyl;

-A- is a diradical -O-, -S-, $-SO_2-$, -SO-, $-SO_2NR^7-$ or $-NR^7SO_2-$ wherein R^7 is hydrogen or (C_1-C_4)-alkyl;

-B is a sulfur or oxygen atom or a $-SO_2-$ or -SO- group or a single bond;

-D is a 5-tetrazolyl or $-COOR^8$ group, wherein R^8 is hydrogen, a (C_1-C_4)-alkyl or a phenylalkyl group of less than 10 carbon atoms;

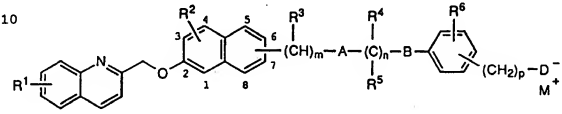
m is an integ r from 0 to 4;

n and p are integers from 0 to 6, with the proviso that

n + p is less or equal to 6.

The present invention also relates to a process for the preparation of the novel naphthalene quinolines, as well as the therapeutical use thereof.

The present invention also relates to the solvates and the pharmaceutically acceptable salts of the quinolines of formula I and particularly the salts represented by formula Ia,



Ia

wherein M^+ is an alkali metal cation (e.g. Na^+, K^+) or represents a half amount of an alkaline-earth metal cation (e.g. 1/2 Ca^{2+}, 1/2 Mg^{2+}), or a cation deriving from an amine or quaternary ammonium salt (such as triethanolammonium, tris(hydroxymethyl)methylammonium).

The compounds of formula I can have one or more asymmetric carbons in their structure. The present invention comprises all the possible stereoisomers as well as the mixtures thereof.

Preferred compounds are those wherein R^2 is hydrogen and D is a 5-tetrazolyl or $COOR^8$ group, wherein R^8 is hydrogen, methyl, ethyl or benzyl.

Also preferred are the compounds of formula I wherein R^1 is hydrogen or chlorine and -A- is -O- or -S-.

Also preferr d are the compounds of formula I

wherein R^1 is hydrogen or chlorine and -A- is $-SO_2NR^7-$ or $-NR^7SO_2-$, wherein R^7 is hydrogen or methyl.

Particularly preferred are the compounds of formula I wherein the substituent containing A is bound to the 7- position of the 2-naphthol ring, R^1 is hydrogen and -A- is -O- or -S-, n and p being integers from 0 to 4.

Particularly preferred are the compounds of formula I wherein the substituent containing A is bound to the 7- position of the 2-naphthol ring, m is 0 and -A- is $-SO_2NR^7-$ or $-NR^7SO_2-$, wherein R^7 is hydrogen or methyl, n and p being integers from 0 to 4.

Particularly preferred compounds of the present invention are the following ones:

4-[3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyl]-benzoic acid;

5-[4-[3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyl]phenyl]-1H-tetrazole;

4-[3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]butyl]-benzoic acid;

4-[2-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]ethoxy]-benzoic acid;

4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]-ethyl]benzoic acid;

4-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxymethyl]-benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonyl-amino]ethyl]benzoic acid;

N-methyl-4-[2-[[7-(2-quinolinyl-methyloxy)-2-naphthyl]-sulfonylamino]ethyl]benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonyl-amino]m thyl]b nzoic acid;

4-[2-hydroxy-3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyloxy]benzoic acid;

5-[4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]phenyl]-1*H*-tetrazole;

3-fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid;

2-fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid;

3-methoxy-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid;

3-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid;

4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethylthio]ethyl]benzoic acid;

3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoic acid;

4-[1-methyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylamino]ethyl]benzoic acid;

4-[1,1-dimethyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylamino]ethyl]benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid;

5-[4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenyl]-1*H*-tetrazole;

3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid;

3-methoxy-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic acid;

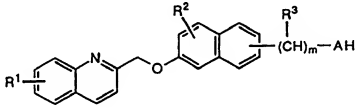
4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylami-

no]propyl]phenylacetic acid;

4-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic acid;

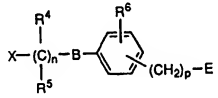
2-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic acid.

According to the present invention the compounds of general formula I wherein A is -O- or -S- are obtained by a process in which a starting compound of general formula II,



II

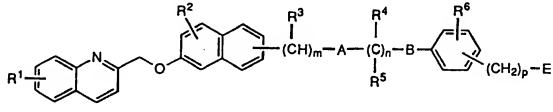
wherein R^1, R^2, R^3 and m have the above defined meanings and A is oxygen or sulfur, is reacted with a compound III,



III

wherein R^4, R^5, R^6, B, n and p have the above defined meanings, X is a chlorine or bromine atom or an alkyl- or arylsulfonate group and E can be equivalent to the group D in I or, when D in formula I is COOH or a 5-tetrazolyl group, then E is CN, or alternatively, when D in formula I is COOH, then E can contain a suitable carboxy-protecting group, for example a methyl, ethyl or benzyl ester. The reaction between II and III is carried

out previously preparing a salt of the alcohol or of the thiol II, by treatment with a suitable base, such as a metal hydride when A is oxygen and m = 1 or a metal hydroxide, alkoxide or carbonate in the other cases, and subsequently reacting the salt of II with compound III in a suitable solvent such as N,N-dimethylformamide, benzene or tetrahydrofuran, at a temperature ranging from 0°C to the solvent reflux, for a time between 3 and 24 hours. A compound of formula IV,

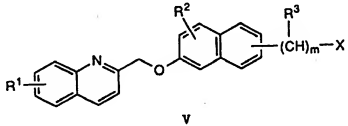


IV

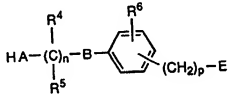
is thereby obtained, which coincides with I or is transformed into I either removing any COOH-protecting groups present in E or hydrolysing the nitrile group present in E to carboxylic acid or converting said nitrile group to a 5-tetrazolyl group by reaction with sodium azide. Therefore, when E is for example a methyl, ethyl or benzyl ester, it can be removed by treatment with a suitable base, such as lithium or sodium hydroxide in aqueous solution in a suitable organic solvent such as methanol, ethanol or tetrahydrofuran, at a temperature from 20°C to the solvent reflux, for a time between 1 and 48 hours. When E is a nitrile group, it can be hydrolyzed to carboxylic acid with 35% NaOH in a suitable organic solvent such as ethanol or dioxane, at the solvent reflux, for a time between 1 and 18

hours. When E is a nitrile group it can be transformed into a 5-tetrazolyl group either by treatment with sodium azide or in the presence of a mild acid such as ammonium chloride or piperidinium chloride, or in the presence of tributyltin chloride, in a suitable organic solvent such as N,N-dimethylformamide, at a temperature from 70° to 150°C, for a time between 5 and 72 hours.

Alternatively, a compound of general formula IV wherein A is oxygen or sulfur can be obtained following the same process as above, starting from the compounds V and VI,



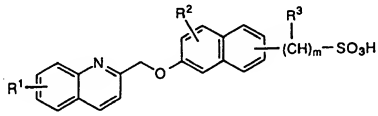
V



VI

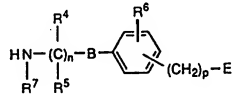
wherein R^1, R^2, R^3, R^4, R^5, R^6, B, X, n, m and p have the above defined meanings, A is oxygen or sulfur and E represents the groups defined above with the exception of the 5-tetrazolyl group.

A compound of general formula I wherein A is $-SO_2-NR^7-$ is obtained by a process in which a starting compound of gen ral formula VII,



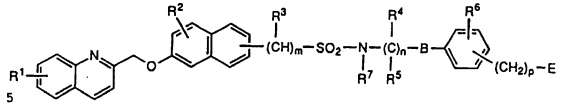
VII

wherein R^1, R^2, R^3 and m have the above defined meanings, is reacted with a compound VIII,



VIII

wherein R^4, R^5, R^6, R^7, B, E, n and p have the above defined meanings. The reaction between VII and VIII is carried out previously preparing the acid chloride of the compound VII by treatment, for example, with phosphorous pentachloride, phosphorous trichloride or thionyl chloride in an inert solvent at a temperature from 25° to 80°C for a time between 1 and 24 hours, and subsequently reacting it with the compound VIII in the presence of a base such as triethylamine, pyridine or 4-dimethylaminopyridine, in a suitable aprotic solvent such as chloroform, methylene chloride or N,N-dimethylformamide, at a temperature from 0° to 80°C for a time between 1 and 24 hours, thereby obtaining a compound of formula IXa,

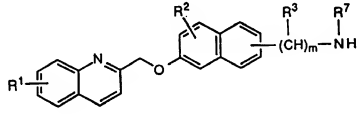


IXa

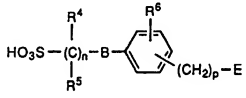
which coincides with I or is converted into I, either removing any COOH-protecting groups present in E, or hydrolysing the nitrile group present in E to carboxylic acid, or converting said nitrile group to a 5-tetrazolyl group by reaction with sodium azide, as described above.

Alternatively, a compound of general formula IXa wherein R^7 is (C_1-C_4)-alkyl can be obtained starting from a compound of formula IXa wherein R^7 is hydrogen by alkylation with a (C_1-C_4)-alkyl bromide or chloride in the presence of a base such as a metal hydride or alkoxide, in a suitable solvent such as N,N-dimethylformamide, tetrahydrofuran or benzene, at a temperature from 25° to 120°C, for a time between 4 and 24 hours.

A compound of general formula I wherein A is $-NR^7-SO_2-$ is obtained following the same process as above, starting from the compounds X and XI,

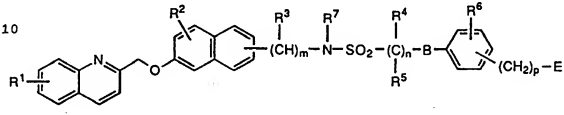


X



XI

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, E, m, n, and p have the above defined meanings, thereby obtaining a compound of formula IXb,



IXb

which coincides with I or is converted into I, either removing any COOH-protecting groups present in E, or by hydrolysis to carboxylic acid of the nitrile group present in E or converting said nitrile group to a 5-tetrazolyl group by reaction with sodium azide, as described above.

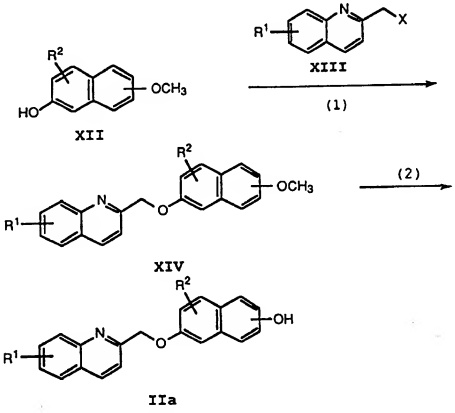
Alternatively, a compound of general formula IXb where R^7 is (C_1-C_4)-alkyl can be obtained starting from a compound of formula IXb where R^7 is hydrogen, following the process described for the preparation of IXa where R^7 is (C_1-C_4)-alkyl, starting from IXa where R^7 is hydrogen.

A compound of general formula I wherein A is $-SO_2-$ or -SO- is obtained starting from a compound IV by reaction with a suitable oxidizing reagent, according to conventional processes described in literature.

A starting product of formula IIa, i.e. of g neral

formula II wherein A is oxygen and m = 0, can be obtained, for example, following the synthetic sequence shown in scheme 1.

Scheme 1

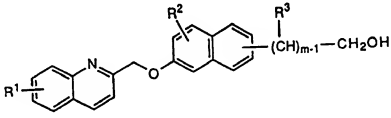


In this sequence, a compound XIV can be obtained, for example, subjecting a compound XII, commercial or easily available by similar chemical processes, to the action of a base such as sodium methoxide or sodium hydride, and subsequently reacting it with a compound XIII, wherein R^1 and X have the above defined meanings, in a suitable organic solvent such as benzene, N,N-dimethylformamide or tetrahydrofuran, at a temperature from 0° to 25°C for a time between 3 and 24 hours (step 1).

A compound IIa can be obtained starting from XIV by

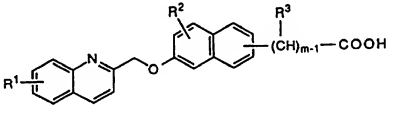
treatment with boron tribromide in a suitable organic solvent, such as chloroform or dichloromethane, at a temperature from -70°C to 25°C for a time between 2 and 24 hours (step 2).

Analogously, a starting compound of formula IIb,



IIb

i.e. of general formula II wherein A is oxygen, m=1 and with no substituents at the methylene bound to the hydroxyl, can be obtained, for example, starting from a compound **XV**,



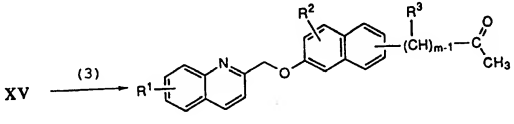
XV

wherein R^1, R^2, R^3 and m have the above defined meanings, by reduction of the carboxylic acid group with a metal hydride, such as lithium aluminum hydride or borane, in a suitable aprotic solvent such as ethyl ether or tetrahydrofuran at a temperature from -10°C to the solvent reflux for a time between 2 and 24 hours.

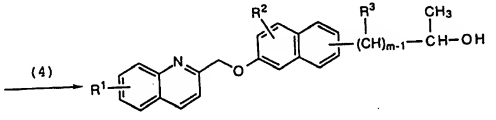
Similarly, a starting compound of formula IIc, i.e. of general formula II wherein A is oxygen, m=1 and where R^3 is methyl bound to the hydroxyl-substituted carbon can be obtained, for example, following the synthetic

sequence shown in the scheme 2.

Scheme 2



XVI



IIc

In such a sequence, a compound XVI can be obtained by reaction of a compound XV with methyl lithium in the presence of trimethylsilyl chloride in a suitable aprotic solvent such as ethyl ether or tetrahydrofuran at a temperature from -10° to 25 °C for a time between 2 and 24 hours.

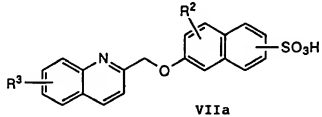
A compound IIc can be obtained, for example, by reduction of a compound XVI by the action of a metal hydride such as sodium borohydride or lithium aluminum hydride in a suitable solvent such as tetrahydrofuran or ethyl ether, at a temperature from 0°C to the solvent reflux and for a time between 2 and 24 hours.

A compound of general formula V where X is an alkyl- or arylsulfonic group can be obtained starting from a compound II by reaction with an alkyl- or arylsulfonyl chloride such as mesyl or tosyl chloride, in the pr sence of a base such as triethylamine or

pyridine, in a suitable solvent such as methylene chloride or chloroform, at a temperature from -30° to 25°C, for a time between 2 and 24 hours.

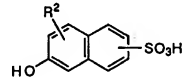
A starting compound of general formula II wherein A is sulfur can be obtained starting from a compound II wherein A is oxygen, following chemical processes similar to those described in literature.

A starting compound of formula VIIa,



VIIa

i.e. of general formula VII with m = 0, can be obtained by reaction of a compound XVII,



XVII

commercial or easily available by similar chemical processes, wherein R^2 represents the groups defined above, with a compound XIII, following the process described for the preparation of XIV starting from XII.

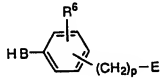
A starting compound of formula VII where m = 1 can be obtained, for example, by reaction of a compound V with a metal sulfite such as sodium sulfite in water or mixtures of water with a miscible organic solvent such as ethanol, methanol or tetrahydrofuran, at the solvent reflux and for a time between 2 and 24 hours.

The starting compounds of formulae X and XV can be

obtained following the synthetic processes described in literature (application nº ES 9401696/8).

A starting compound III where X is an alkyl- or arylsulfonate group can be obtained by reaction of a compound VI with an alkyl- or arylsulfonyl chloride in the conditions described for the preparation of V starting from II.

Analogously, a compound III where X is a chlorine or bromine atom and B is an oxygen or sulfur atom can be obtained by reaction of a compound XVIII,



XVIII

commercial or easily available by similar chemical processes, wherein R^6 and p have the above defined meanings, E represents the groups defined above with the exception of the 5-tetrazolyl group and B is an oxygen or sulfur atom, with a compound XIX,

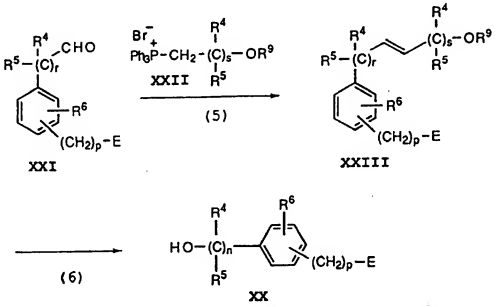
XIX

wherein R^4, R^5, X and n have the above defined meanings, following the process described above for the preparation of IV starting from II and III.

A starting compound of formula XX, i.e. of gen ral

formula VI where B is a single bond and A is an oxygen atom, can be prepared, when not commercially available, according to the synthetic sequence represented in scheme 3.

Scheme 3

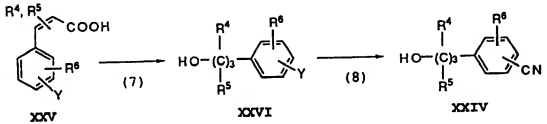


A compound XXIII can be prepared starting from the compounds XXI and XXII, commercial or easily available following simple chemical processes, wherein R^4 and R^5 have the above defined meanings, E represents the groups defined above with the exception of nitrile, r and s are integers from 0 to 4 so that r+s+2 = n and R^9 is a suitable hydroxy-protecting group, easily removable by catalytic hydrogenation, such as the benzyl group. The reaction between XXI and XXII (step 5) is carried out in the conditions usually described for the Wittig reaction, in the presence of a suitable base such as lithium bis(trimethylsilyl)amide, in a suitable solvent such as ethyl ether or tetrahydrofuran, at a temperature from 25°C to the solvent reflux, for a time between 45

minutes and 18 hours. Starting from a compound XXIII, a compound XX can be obtained by catalytic hydrogenation under room pressure and temperature, in the presence of palladium hydroxide, in a metanol:water mixture and for a time between 8 and 24 hours (step 6).

Alternatively, a starting compound of formula XXIV, i.e. of general formula VI where n = 3, p = 0, A is oxygen, B is a single bond and E is a nitrile group, can be obtained according to the synthetic sequence shown in scheme 4.

Scheme 4



XXV XXVI XXIV

In such a sequence, starting from a compound XXV, commercial or easily available by similar chemical processes, wherein R^4 and R^5 have the above defined meanings and Y is a chlorine or bromine atom, a compound XXVI can be prepared by reduction with a metal hydride, such as lithium aluminum hydride, in a suitable solvent such as ethyl ether or tetrahydrofuran, at a temperature between 25°C and the solvent reflux, for a time between the 3 and 8 hours (step 7). A compound XXIV can be obtained by reaction of a compound XXVI with CuCN in a high boiling solvent such as N-methylpyrrolidone at a temperature from 180° to 220°C for a time between 1 and 4 hours (st p 8).

A starting compound of formula VI wherein A is a sulfur atom can be obtained starting from a compound VI wherein A is oxygen, following similar chemical processes described in literature.

A starting compound VIII where R^4 and R^5 are hydrogen, can be obtained following similar chemical processes described in literature (see Spanish Application 9401696/8 from the same applicants).

A starting compound XI can be prepared starting from a compound VI following the process described above for the preparation of VII starting from V.

The compounds of the present invention show a remarkable antagonistic activity of leukotrienes effects and they have therefore anti-inflammatory and anti-allergic properties which make them useful in the treatment of diseases wherein those mediators are involved. Said compounds can be therefore used in human therapy, for the prevention and treatment of allergic rhinitis, bronchial asthma, hypersensitivity reactions such as allergic conjunctivitis, various inflammatory conditions such as rheumatoid arthritis, osteoarthritis, tendinitis, bursitis, psoriasis and related inflammations.

The compound of the present invention may also be used in the treatment of diseases of the cardiovascular system, such as cardiac ischemia, myocardic infarct, coronary spasm, cardiac anaphylaxis, cerebral oedema and endotoxyc schock.

For the intended therapeutic uses, the compounds of the invention are formulated in suitable pharmaceutical compositions, using conventional techniques and methods,

as disclosed in Remington's Pharmaceutical Science Handbook, Mack Pub. Co., N.Y. U.S.A. Examples of said formulations include capsules, tablets, syrups and the like, containing from 1 to 1000 mg of active principle per unit dose.

EXAMPLES

The following examples illustrate the preparation of the compounds of the present invention.

Example 1: 4-[3-[7-(Quinolinylmethyloxy)-2-naphthyloxyl-propyl]benzoic acid

1A 2-(7-Methoxy-2-naphthyloxymethyl)quinoline

A 25% sodium methoxide solution in methanol (2.48 ml, 43.4 mmol) was added to a solution of 7-methoxy-2-naphthol (7.55 g, 43.4 mmol) in DMF (200 ml) stirring at room temperature for 15 min. After that 2-chloromethylquinoline (7.70 g, 43.4 mmol) was added stirring at room temperature for 18 h. Subsequently the solution was evaporated to dryness, the residue was dissolved in ethyl acetate (250 ml), washed with 5% $NaHCO_3$ (3x25 ml), dried and the solvent was evaporated off, to obtain a crude which was purified by chromatography through a silica gel column eluting with petroleum ether:ethyl acetate mixtures of increasing polarity. 9.55 g of the title product were thereby obtained (70% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.87 (s, 3H); 5.50 (s, 2H); 7.00 (m, 2H); 7.17 (m, 2H); 7.55 (t, 1H); 7.63-7.79 (sc, 4H); 7.82 (d, 1H); 8.13 (d, 1H); 8.19 (d, 1H).

1B 7-(2-Quinolinylmethyloxy)-2-naphthol

A solution of 1M boron tribromide in dichloromethane (57 ml) was added at -30°C to a solution

of 2-(7-methoxy-2-naphthyloxymethyl)-quinoline (9.55 g, 30.3 mmol) in dichloromethane (100 ml). The mixture was left to cool, stirring for 5 hours at room temperature. Subsequently, methanol (70 ml) was added, stirring for 1 h. After that the mixture was evaporated to dryness, the residue was dissolved in ethyl acetate (250 ml), washed with 2% $NaHCO_3$ (1x30 ml), dried and the solvent was evaporated off, to obtain a crude which was purified by crystallization in methanol, thereby obtaining 4.14 g of the title compound as a yellow solid (45% yield).

^1H N.M.R. (300 MHz, $CDCl_3/CD_3OD$ mixtures) δ ppm: 5.45 (s, 2H); 6.91 (dd, 1H); 7.00 (d, 1H); 7.09 (dd, 1H); 7.12 (d, 1H); 7.61-7.85 (sc, 5H); 7.95 (d, 1H); 8.09 (d, 1H); 8.37 (d, 1H).

1C 3-(4-Bromophenyl)propan-1-ol

To a suspension of lithium aluminum hydride (2.49 g, 66 mmol) in dry ethyl ether (130 ml) was added under inert atmosphere a solution of 4-bromocinnamic acid (5.0 g, 22 mmol) in 20 ml of dry ethyl ether, stirring at room temperature for 2 hours. Subsequently, a NaCl aqueous saturated solution (80 ml) was slowly added, the two phases were separated and the aqueous one was extracted with ethyl acetate (3x50 ml). The organic extracts were dried and the solvent was evaporated off to obtain 3.60 g of the title compound as a yellowish oil (76 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.85 (m, 2H); 2.66 (t, 2H); 3.65 (t, 2H); 7.06 (d, 2H); 7.39 (d, 2H).

1D 4-(3-Hydroxypropyl)benzonitrile

A mixture of 3-(4-bromophenyl)propan-1-ol (2.0 g, 9.3 mmol), copper (I) cyanide (1.49 g, 16.7 mmol) and N-

methylpyrrolidinone (13 ml) was left under stirring at 200°C for 2.5 hours. Subsequently the reaction mixture was cooled to room temperature, poured onto a solution of diethylamine (30 g) and water (80 ml) and extracted with ethyl acetate (3x40 ml). The combined organic phases were dried and the volatiles were evaporated off, to obtain an oil from which N-methylpyrrolidinone was removed by distillation under high vacuum (0.5 torr, 85°C), thereby obtaining 0.78 g of the title compound (52 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.85 (m, 2H); 2.42 (s broad, 1H); 2.76 (t, 2H); 3.64 (t, 2H); 7.29 (d, 2H); 7.53 (d, 2H).

1E 3-(4-Cyanophenyl)propyl methanesulfonate

Triethylamine (0.54 ml, 4.03 mmol) and methanesulfonyl chloride (0.30 ml, 4.03 mmol) were added to a solution of 4-(3-hydroxypropyl)benzonitrile (0.50 g, 3.10 mmol) in dry methylene chloride (15 ml), cooled at 0°C and under inert atmosphere. The mixture was left under stirring at 0°C for 2 hours. After that it was diluted with methylene chloride (50 ml), washed successively with 0.05M HCl, with a NaCl saturated solution, dried and the solvent was evaporated off, thereby obtaining 0.675 g of the title compound as a semi-solid oil (94 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.89 (m, 2H); 2.63 (t, 2H); 2.85 (s, 3H); 4.05 (t, 2H); 7.14 (d, 2H); 7.38 (d, 2H).

1F 4-[3-[7-(Quinolinylmethyloxy)-2-naphthyloxy]propyl]-benzonitrile

Following the process described in point A,

starting from 7-(2-quinolinylmethyloxy)-2-naphthol and 3-(4-cyanophenyl)propyl methanesulfonate, the title compound was prepared and purified by chromatography through a silica gel column eluting with petroleum ether:chloroform, 1:1, (40% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.99 (m, 2H); 2.76 (t, 2H); 3.88 (t, 2H); 5.38 (s, 2H); 6.83 (d, 1H); 6.87 (dd, 1H); 7.01 (d, 1H); 7.05 (dd, 1H); 7.17 (d, 2H); 7.43 (m, 3H); 7.53-7.59 (m, 3H); 7.63 (dt, 1H); 7.69 (d, 1H); 8.00 (d, 1H); 8.04 (d, 1H).

1G 4-[3-[7-(Quinolinylmethyloxy)-2-naphthyloxy]-propyl]-benzoic acid

A solution of 35% NaOH (22 ml) was added to a solution of 4-[3-[7-(quinolinylmethyloxy)-2-naphthyl-oxy]propyl]-benzonitrile (635 mg, 1.43 mmol) in ethanol (50 ml) refluxing for 8 h. After that the mixture was acidified with 1M HCl to pH of about 5 and the precipitated solid was recovered by filtration, thereby obtaining 391 mg of the title compound as a yellow solid with melting point 197°-198°C. (59% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.09 (m, 2H); 2.85 (t, 2H); 4.05 (t, 2H); 5.47 (s, 2H); 7.00 (dd, 1H); 7.16 (d, 2H); 7.34 (dd, 1H); 7.37 (d, 2H); 7.63 (dt, 1H); 7.70-7.79 (m, 3H); 7.80 (dt, 1H); 7.87 (d, 2H); 8.01 (d, 1H); 8.05 (d, 1H); 8.43 (d, 1H).

Example 2: 5-[4-[3-[7-(2-Quinolinylmethyloxy)-2-naphthyloxy]propyl]phenyl]-1*H*-tetrazole

Tributyltin chloride (0.74 ml, 2.74 mmol) was added under inert atmosphere to a suspension of sodium azide (178 mg, 2.74 mmol) in dry toluene (20 ml), stirring at room temperature for 30 min. Subsequently a solution of

4-[3-[7-(quinolinylmethyloxy)-2-naphthyloxy]propyl]benzonitrile (338 mg, 0.76 mmol) in DMF (4 ml) was added, stirring for 73 hours at 100°C. After this time, the mixture was left to cool at room temperature and a mixture of methanol (9 ml) and 1M HCl (1 ml) was added. After 1h stirring at room temperature, the mixture was diluted with ethyl acetate, washed with a NaCl saturated solution, dried and the solvent was evaporated off. The resulting residue was purified by chromatography through a silica gel column eluting with chloroform:methanol, 9:1, followed by digestion in methanol, thereby obtaining 59 mg of the title compound as a yellowish solid with melting point 192.3°-193.5°C.

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.12 (m, 2H); 2.87 (t, 2H); 4.07 (t, 2H); 5.47 (s, 2H); 7.00 (dd, 1H); 7.14 (dd, 1H); 7.17 (d, 1H); 7.34 (d, 1H); 7.48 (d, 2H); 7.62 (dt, 1H); 7.70-7.82 (m, 4H); 7.96 (d, 2H); 8.00 (d, 1H); 8.05 (d, 1H); 8.43 (d, 1H).

Example 3: 4-[3-[7-(Quinolinylmethyloxy)-2-naphthyloxyl-butyl]benzoic acid

3A Methyl 4-(4-benzyloxy-1-butenyl)benzoate

Lithium bis(trimethylsilyl)amide (3.35 ml, 3.35 mmol) was added to a solution of (3-benzyloxypropyl)triphenylphosphonium bromide (1.5 g, 3.05 mmol) in dry tetrahydrofuran (20 ml), stirring at room temperature for 15 min. Subsequently a solution of methyl 4-formylbenzoate (0.40 g, 2.44 mmol) in tetrahydrofuran (minimum amount for the solution) stirring for 30 min. at room temperature. After that the mixture was diluted with tetrahydrofuran (20 ml), washed successively with 0.1M HCl and water, dried and the

solvent was evaporated off, to obtain a residue which was purified by chromatography through a silica gel column eluting with petroleum ether:ethyl ether, 8:2, thereby obtaining 0.60 g of the title compound as a colourless oil (67% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.69 (m, 2H); 3.59 (t, 2H); 3.90 (s, 3H); 4.53 (s, 1H); 5.87 (m, 1H); 6.50 (m, 1H); 7.30-7.40 (sc, 7H); 8.04 (d, 2H).

3B Methyl 4-(4-hydroxybutyl)benzoate

10% $Pd(OH)_2$ on carbon was added to a solution of methyl 4-(4-benzyloxy-1-butenyl)benzoate (519 mg, 1.80 mmol) in a methanol:water, 9:1 mixture (30 ml), stirring at room temperature for 18 h, under hydrogen atmosphere. Subsequently the catalyst was filtered off and the filtrate was evaporated to dryness, to obtain 209 mg of the title compound as a colourless oil (58% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.72 (m, 2H); 1.83 (m, 2H); 2.80 (t, 2H); 3.77 (t, 2H); 4.03 (s, 3H); 7.37 (d, 2H); 8.08 (d, 2H).

3C Methyl 4-[4-(Methylsulfonyloxy)butyl]benzoate

Triethylamine (0.16 ml, 1.24 mmol) and methanesulfonyl chloride (0.112 ml, 1.24 mmol) were added to a solution of methyl 4-(4-hydroxybutyl)benzoate (200 mg, 0.96 mmol) in dry methylene chloride (15 ml), cooled at 0°C and under inert atmosphere. The mixture was stirred at 0°C for 2 hours, then diluted with methylene chloride (50 ml), washed successively with 0.05M HCl and with a NaCl saturated solution, dried and the solvent was evaporated off, to obtain a residue which was purified by chromatography through a silica gel column eluting with petroleum ether:chloroform, 7:3,

thereby obtaining 190 mg of the title compound as a colourless oil (70 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.76 (m, 4H); 2.70 (t, 2H); 2.97 (s, 3H); 3.89 (s, 3H); 4.22 (t, 2H); 7.23 (d, 2H); 7.94 (d, 2H).

3D Methyl 4-[3-[7-(Quinolinylmethyloxy)-2-naphthyloxyl-butyl]-benzoate

Following the process described in example 1 (point B), starting from 7-(2-quinolinylmethyloxy)-2-naphthol and methyl 4-[4-(methylsulfonyloxy)butyl]benzoate, the title compound was prepared (50% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.82 (m, 4H); 2.74 (t, 2H); 3.87 (s, 3H); 4.02 (t, 2H); 5.47 (s, 2H); 6.94 (d, 1H); 6.95 (dd, 1H); 7.10 (d, 1H); 7.12 (dd, 1H); 7.25 (d, 2H); 7.53 (t, 1H); 7.60-7.76 (sc, 4H); 7.81 (d, 1H); 7.93 (d, 2H); 8.09 (d, 1H); 8.16 (d, 1H).

3E 4-[3-[7-(Quinolinylmethyloxy)-2-naphthyloxyl-butyl]-benzoic acid

A 1M solution of potassium hydroxide (1.52 ml) was added to a solution of methyl 4-[3-[7-(quinolinylmethyloxy)-2-naphthyloxy]butyl]-benzoate (0.150 mg, 0.31 mmol) in ethanol (7 ml). The mixture was stirred under reflux for 2 h, after that was neutralized with 1M HCl and ethanol was removed. The resulting crude was suspended in water (30 ml) and extracted with ethyl acetate (4x30 ml). The organic phase was dried and the solvent was evaporated off, to obtain 102 mg of the title compound as a yellowish solid with melting point 197.9°-199.9°C (69% yield).

^1H N.M.R. (300 MHz, DMSO) δ ppm: 1.77 (m, 4H); 2.73 (t broad, 2H); 4.07 (t broad, 2H); 5.48 (s, 2H); 6.99 (dd,

1H); 7.14 (dd, 1H); 7.18 (d, 1H); 7.28 (d, 2H); 7.33 (d, 1H); 7.63 (dt, 1H); 7.70-7.80 (m, 4H); 7.87 (d, 2H); 8.01 (d, 1H); 8.05 (d, 1H); 8.43 (d, 1H).

Example 4: 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthyl-oxy]ethoxy]benzoic acid

4A Methyl 4-hydroxybenzoate

Concentrated sulfuric acid (56 ml) was added to a solution of 4-hydroxybenzoic acid (10 g, 72.4 mmol) in methanol (420 ml), stirring under reflux for 2 h. After that, the volatiles were evaporated off under reduced pressure and the resulting residue was neutralized with a sodium bicarbonate saturated solution and extracted with ethyl ether (4x100 ml). The mixture was dried and solvent evaporated off under reduced pressure, to obtain 10.79 g of the title compound as a white solid (98% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.57 (s, 3H); 6.56 (d, 2H); 7.60 (d, 2H).

4B Methyl 4-(2-bromoethyloxy)benzoate

A solution of KOH (3.69 g, 32.9 mmol) in dimethylsulfoxide (10 ml) was added to a solution of methyl 4-hydroxybenzoate (5.0 g, 32.9 mmol) in dimethylsulfoxide (10 ml), stirring at room temperature for 15 min. Subsequently 1,2-dibromoethane (5.67 ml, 32.9 mmol) was added, stirring at room temperature for 18 h. After that the mixture was diluted with water (50 ml) and extracted with ethyl ether. The mixture was dried and the solvent was evaporated off to obtain a residue which was purified by chromatography through a silica gel column eluting with mixtures of n-hexane:chloroform of increasing polarity, thereby

obtaining 1.99 g of the title compound (23% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.67 (t, 2H); 3.90 (s, 3H); 4.35 (t, 2H); 6.93 (d, 2H); 8.01 (d, 2H).

4C Methyl 4-[2-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]ethoxy]-benzoate

Following the process described in point B, starting from 7-(2-quinolinylmethyloxy)-2-naphthol and methyl 4-(2-bromoethyloxy)benzoate, the title compound was prepared, which was purified by crystallization in methanol (66% yield).

^1H N.M.R. (300 MHz, DMSO) δ ppm: 3.82 (s, 3H); 4.45 (m, 4H); 5.48 (s, 2H); 7.04 (dd, 1H); 7.12 (d, 2H); 7.18 (dd, 1H); 7.26 (d, 1H); 7.35 (d, 1H); 7.63 (t, 1H); 7.71-7.82 (m, 4H); 7.93 (d, 2H); 8.02 (d, 1H); 8.06 (d, 1H); 8.44 (d, 1H).

4D 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthyloxy]-ethoxy]benzoic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]ethoxy]benzoate, the title compound was prepared as a white solid with melting point 231°-233°C, and purified by digestion in methanol.

^1H N.M.R. (300 MHz, DMSO) δ ppm: 4.43 (s broad, 4H); 5.49 (s, 2H); 7.03 (dd, 1H); 7.08 (d, 2H); 7.16 (dd, 1H); 7.26 (d, 1H); 7.35 (d, 1H); 7.62 (t, 1H); 7.71-7.82 (m, 4H); 7.92 (d, 2H); 8.00 (d, 1H); 8.06 (d, 1H); 8.42 d, 1H).

Example 5: 4-[2-Hydroxy-3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyloxy]benzoic acid

5A Methyl 4-(2,3-epoxypropyloxy)benzoate

Potassium carbonate (4.69 g, 17 mmol) was added to

a solution of methyl 4-hydroxybenzoate (2.61 g, 17 mmol) in N,N-dimethylformamide (75 ml) stirring at room temperature for 10 minutes. After that, 1,3-dibromo-2-propanol (3.74 g, 17 mmol) was added and the mixture was left under stirring at 60°C for 5 h. Subsequently water (50 ml) was added and the mixture was extracted with ethyl ether (3x75 ml). The solution was dried and the solvents were evaporated off to obtain 2.50 g of the title compound (70% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.76 (dd, 1H); 2.91 (dd, 1H); 3.35 (m, 1H); 3.86 (s, 3H); 3.96 (dd, 1H); 4.28 (dd, 1H), 6.92 (d, 2H); 7.96 (d, 2H).

5B Methyl 4-[2-hydroxy-3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyloxy]benzoate

A dispersion of sodium hydride (62 mg, 1.56 mmol) in 60% mineral oil was washed by decantation with anhydrous hexane, then it was resuspended dry N,N-dimethylformamide (25 ml). The resulting suspension was added at 0°C and under inert atmosfere to a solution 7-(2-quinolinylmethyloxy)-2-naphthol (469 mg, 1.56 mmol) in N,N-dimethylformamide (10 ml) stirring at room temperature for 30 min. After that methyl 4-(2,3-epoxypropyloxy)benzoate (250 mg, 1.20 mmol). The mixture was stirred at room temperature for 24 h. Subsequently water was added (50 ml) and the mixture was extracted with ethyl acetate (4x50 ml). The organic phase was dried and the solvent was removed under reduced pressure, to obtain a crude which was purified by chromatography through a silica gel column eluting with mixtures of n-hexane:chloroform of increasing polarity. 190 mg of the title compound were thereby obtained (31%

yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.82 (s, 3H); 4.15 (m, 4H); 4.41 (m, 1H); 5.42 (s, 2H); 6.87 (d, 2H); 6.90-7.12 (sc, 4H); 7.45-7.80 (sc, 5H); 7.91 (m, 3H); 8.00 (d, 1H); 8.04 (d, 1H).

5C 4-[2-Hydroxy-3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyloxy]benzoic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-hydroxy-3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyloxy]benzoate, the title compound was prepared as a white solid with melting point 212-214°C.

^1H N.M.R. (300 MHz, DMSO) δppm: 4.05-4.21 (m, 5H); 5.43 (s, 3H); 7.00 (m, 3H); 7.11 (dd, 1H); 7.18 (s, 1H); 7.31 (s, 1H); 7.58 (t, 1H); 7.72 (m, 4H); 7.84 (d, 2H); 7.96 (d, 1H); 8.01 (d, 1H), 8.38 (d, 1H).

Example 6: 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid

6A 7-Methoxy-2-trifluoromethylsulfonyloxynaphthalene

Pyridine (6.87 ml) and trifluoromethanesulfonic anhydride (10 ml, 59.0 mmol) were added to a solution of 7-methoxy-2-naphthol (8.5 g, 46.7 mmol) in methylene chloride (150 ml), cooled at 0°C and under inert atmosphere. The mixture was left under stirring at this temperature for 1 h, then was diluted with ethyl ether (100 ml), washed in succession with 0.01M HCl, a $NaHCO_3$ saturated solution and NaCl saturated solution, dried and the solvent was removed, to obtain 15.1 g of the title compound as an orange oil (97 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.83 (s, 3H); 7.03 (d, 1H); 7.14 (dd, 2H); 7.58 (d, 1H); 7.66 (d, 1H); 7.71 (d,

1H).

6B Methyl 7-methoxy-2-naphtalenecarboxylate

A solution of 7-methoxy-2-trifluoro-methylsulfonyl-oxynaphthalene (15.0 g, 47.5 mmol) in absolute methanol (95 ml) was added with triethylamine (28 ml), dimethyl-sulfoxide (140 ml), $Pd(OAc)_2$ (0.319 g, 1.43 mmol) and 1,3-bis(diphenylphosphine)propane (0.580 g, 1.43 mmol). A carbon monoxide stream was bubbled for 4 min, heating at 75°C for 3 h under carbon monoxide atmosphere. Then the mixture was cooled at room temperature, filtered through celite and methanol was evaporated off. The re-sulting solution was diluted with ethyl ether and was washed in seccsion with water, 5% HCl, a 5% $NaHCO_3$ solu-tion and a NaCl saturated solution, dried and the sol-vent was evaporated off, to obtain a crude which was purified by flash chromatography through a silica gel column. Eluting with petroleum ether:ethyl ether, 75:25, 6.46 g of the title compound were obtained (64% yield). ^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.92 (s, 3H); 3.97 (s, 3H); 7.22 (d, 1H); 7.24 (dd, 1H); 7.76 (d, 1H); 7.79 (d, 1H); 7.92 (dd, 1H); 8.50 (s, 1H).

6C Methyl 7-hydroxy-2-naphtalenecarboxylate

Following the process described in example 1 (point B), starting from methyl 7-methoxy-2-naphtalenecarboxy-late, the title compound was prepared (90% yield). ^1H N.M.R. (300 MHz, CD_3OD) δ ppm: 3.99 (s, 3H); 7.24 (dd, 1H); 7.26 (s, 1H); 7.82 (m, 3H); 8.41 (s, 1H).

6D Methyl 7-(2-quinolinylmethyloxy)-2-naphtalenecarboxy-late

Following the process described in example 1 (point A), starting from methyl 7-hydroxy-2-naphtalenecarboxy-

late, the title compound was prepared (97 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.98 (s, 3H); 5.55 (s, 2H); 7.36 (d, 1H); 7.43 (dd, 1H); 7.59 (dt, 1H); 7.81 (m, 5H); 7.95 (dd, 1H); 8.16 (d, 1H); 8.23 (d, 1H); 8.47 (s, 1H).

6E 7-(2-Quinolinylmethyloxy)-2-naphtalenecarboxylic acid

Following the process described in example 3 (point E), starting from methyl 7-(2-quinolinylmethyloxy)-2-naphtalenecarboxylate, the title compound was prepared (95% yield).

^1H N.M.R. (300 MHz, CD_3OD) δ ppm: 5.52 (s, 2H); 7.41 (s, 1H); 7.43 (dd, 1H); 7.62 (dt, 1H); 7.77-7.95 (sc, 6H); 8.11 (d, 1H); 8.32 (d, 1H); 8.49 (s, 1H).

6F 7-(2-Quinolinylmethyloxy)-2-naphthylmethanol

A solution of 1M borane in tetrahydrofuran (6.56 ml, 6.56 mmol) was added to a solution of 7-(2-quinolinylmethyloxy)-2-naphtalenecarboxylic acid (1.0 g, 3.04 mmol) in tetrahydrofuran (15 ml), stirring at room temperature for 18 h. Subsequently, a NaCl saturated solution was added, the phases were separated and the organic phase was dried and the solvent was evaporated off, to obtain a residue which was purified by chromatography through a silica gel column eluting with chloroform:methanol, 98:2 (59% yield).

^1H N.M.R. (300 MHz, CD_3OD) δ ppm: 4.69 (s, 2H); 5.39 (s, 2H); 7.24 (dd, 1H); 7.28 (d, 1H); 7.31 (dd, 1H); 7.57 (dt, 1H); 7.65-7.79 (sc, 5H); 7.88 (d, 1H); 8.04 (d, 1H); 8.30 (d, 1H).

6G 7-(2-Quinolinylmethyloxy)-2-naphthylmethyl methanesulfonate

Following the proc ss described in example 1 (point

E), starting from 7-(2-quinolinylmethyloxy)-2-naphthylmethanol, the title compound was prepared (55% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.90 (s, 3H); 5.35 (s, 2H); 5.56 (s, 2H); 7.25 (s, 1H); 7.28 (dd, 1H); 7.31 (dd, 1H); 7.60 (dt, 1H); 7.70-7.90 (sc, 6H); 8.20 (d, 1H); 8.28 (d, 1H).

6H 4-(2-Hydroxyethyl)benzonitrile

A mixture of 2-(4-bromophenyl)ethyl alcohol (1 g, 4.96 mmol), copper (I) cyanide (0.797 g, 8.89 mmol) and N-methylpyrrolydinone (6 ml) was refluxed for 3 h. After that, the reaction crude was poured onto a 8% ethylenediamine aqueous solution (15 ml), extracted with ethyl ether (3x20 ml), the volatiles were evaporated off and N-methylpyrrolydinone was distilled under reduced pressure (0.1 torr), thereby obtaining 0.722 g of the title compound (99% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.89 (t, 2H); 3.84 (t, 2H); 7.35 (d, 2H); 7.56 (d, 2H).

6I 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxy]-ethyl]benzonitrile

A dispersion of potassium hydride (0.608 g, 5.36 mmol) in 35% mineral oil was washed by decantation with anhydrous hexane and, subsequently, resuspended in anhydrous benzene (25 ml). The resulting suspension was added at 0°C and under inert atmosphere to a solution of 4-(2-hydroxyethyl)benzonitrile (0.722 mg, 5.34 mmol) in benzene (10 ml), stirring at room temperature for 15 min. After that, 7-(2-quinolinylmethyloxy)-2-naphthylmethyl methanesulfonate (1.66 g, 4.46 mmol) was added the mixture was left under stirring at room temperature for 18 h, the water (50 ml) was added and the mixture

was extracted with ethyl acetate (4x50 ml). The organic phase was dried and the solvent was evaporated off, to obtain a crude which was purified by chromatography through a silica gel column, eluting with mixtures of petroleum ether:chloroform of increasing polarity, thereby obtaining 0.654 g of the title compound as a yellowish oil (33% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.89 (t, 2H); 3.64 (t, 2H); 4.54 (s, 2H); 5.45 (s, 2H); 7.14 (s, 1H); 7.16 (dd, 1H); 7.21-7.26 (m, 3H); 7.47-7.52 (m, 4H); 7.63-7.71 (m, 4H); 7.76 (d, 1H); 8.06 (d, 1H); 8.12 (d, 1H).

6J 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxyl-ethyl]benzoic acid

Following the process described in example 1 (point G), starting from 4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile, the title compound was prepared as a white solid with melting point 243.2°-245.2°C, which was purified by crystallization in methanol (64% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.89 (t, 2H); 3.68 (t, 2H); 4.61 (s, 2H); 5.50 (s, 2H); 7.19 (d, 2H); 7.27 (d, 1H), 7.30 (d, 1H); 7.43 (s, 1H); 7.63 (t, 1H); 7.66 (s, 1H); 7.73-7.86 (sc, 6H); 8.01 (d, 1H), 8.06 (d, 1H); 8.43 (d, 1H).

Example 7: 4-[[7-(2-Quinolinylmethyloxy)-2-naphthyl-methyloxylmethyl]benzoic acid

7A Methyl 4-(methylsulfonyloxymethyl)benzoate

Following the process described in example 1 (point E), starting from methyl 4-(hydroxymethyl)benzoate, the title compound was prepared (85% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.04 (s, 3H); 3.98 (s,

3H); 5.34 (s, 2H); 7.54 (d, 2H); 8.13 (d, 2H).

7B Methyl 4-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxymethyl]benzoate

Following the process described in example 6 (point I), starting from 7-(2-quinolinylmethyloxy)-2-naphthylmethanol and methyl 4-(methylsulfonyloxymethyl)benzoate, the title compound was prepared and purified by chromatography through a silica gel column, eluting with mixtures of petroleum ether:chloroform of increasing polarity (56% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.90 (s, 3H); 4.59 (s, 2H); 4.69 (s, 2H); 4.50 (s, 2H); 7.21-7.36 (m, 4H); 7.41 (d, 1H); 7.54 (t, 1H); 7.69-7.83 (sc, 8H); 8.09 (d, 1H); 8.18 (d, 1H).

7C 4-[[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxyl-methyl]benzoic

Following the process described in example 3 (point E), starting from methyl 4-[[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]methyl]benzoate, the title compound was prepared as a white solid with melting point 249°-252°C which was purified by crystallization in methanol (70% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 4.52 (s, 2H); 4.61 (s, 2H); 5.45 (s, 2H); 7.22-7.31 (m, 4H); 7.44 (d, 1H); 7.58 (t, 1H); 7.69-7.83 (sc, 7H); 7.96 (d, 1H); 8.01 (d, 1H); 8.39 (d, 1H).

Example 8: 5-[4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxylethyl]phenyl]-1*H*-tetrazole

Following the process described in example 2, starting from 4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile, the title compound was

prepared as a yellowish solid with melting point 181-183°C.

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.97 (t, 2H); 3.74 (t, 2H); 4.62 (s, 2H); 5.48 (s, 2H); 7.26 (dd, 1H); 7.30 (dd, 1H), 7.41 (s, 1H); 7.49 (d, 2H); 7.63 (t, 1H); 7.66 (s, 1H); 7.73 (d, 1H); 7.74-7.94 (sc, 5H); 8.00 (d, 1H), 8.05 (d, 1H); 8.43 (d, 1H).

Example 9: 3-Fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid

9A 4-Bromo-2-fluorobenzyl bromide

N-Bromosuccinimide (5.3 g, 29.1 mmol) and some crystals of dibenzoyl peroxide were added to a solution of 4-bromo-2-fluorotoluene (5 g, 26.5 mmol) in dry carbon tetrachloride (100 ml). The mixture was refluxed for 4 h, then cooled at room temperature, the formed precipitate was filtered off and the filtrate was washed in succession with a 5% sodium thiosulfate solution (1x20ml) and a NaCl saturated solution (2x20 ml), dried and the solvent was evaporated off, thereby obtaining 7.07 g of the title compound as an orange oil (quantitative yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 4.41 (s, 2H); 7.20-7.40 (sc, 3H).

9B 4-Bromo-2-fluorophenylacetonitrile

4-Bromo-2-fluorobenzyl bromide (7.07 g, 26.5 mmol) dissolved in ethanol (12 ml) was added to a solution of sodium cyanide (4.0 g, 81.6 mmol) in water (5 ml), stirring at 100°C for 3 h. After that, the mixture was cooled at room temperature, added with ethyl ether (30 ml) and washed with a NaCl saturated solution (20 ml). The two phases were separated and the aqueous phase was ex-

tracted with ethyl ether (3x25 ml). The ether extracts were dried and the solvent was evaporated off under reduced pressure, to obtain a crude which was purified by flash chromatography through a silica gel column. Eluting with petroleum ether:ethyl ether, 98:2, 4.30 g of the title compound were obtained as an orange oil (76 % yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.61 (s, 2H); 7.09-7.18 (sc, 3H).

9C 4-Bromo-2-fluorophenylacetic acid

Following the process described in example 1 (point G), starting from 4-bromo-2-fluorophenylacetonitrile, the title compound was prepared (95% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.61 (s, 2H); 7.12-7.24 (sc, 3H).

9D Methyl 4-bromo-2-fluorophenylacetate

Following the process described in example 4 (point A), starting from 4-bromo-2-fluorophenylacetic acid, the title compound was prepared (90% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.61 (s, 2H); 3.71 (s, 3H); 7.14 (t, 1H); 7.24 (m, 2H).

9E 2-(4-Bromo-2-fluorophenyl)ethanol

Following the process described in example 1 (point C), starting from methyl 4-bromo-2-fluorophenylacetate, the title compound was prepared (60% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.75 (t, 2H); 3.68 (t, 2H); 4.12 (s broad, 1H); 7.03 (t, 1H); 7.13 (m, 2H).

9F 3-Fluoro-4-(2-hydroxyethyl)benzonitrile

Following the process described in example 6 (point H), starting from 2-(4-bromo-2-fluorophenyl)ethanol, the title compound was prepared which was purified by chro-

matography through a silica gel column eluting with dichloromethane (50% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.27 (t broad, 1H); 2.95 (t, 2H); 3.87 (dt, 2H); 7.30 (d, 1H); 7.39 (m, 2H).

9G 3-Fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile

Following the process described in example 6 (point I), starting from 7-(2-quinolinylmethyloxy)-2-naphthylmethyl methanesulfonate and 3-fluoro-4-(2-hydroxyethyl)benzonitrile, the title compound was prepared (35% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.97 (t, 2H); 3.69 (t, 2H); 4.58 (s, 2H); 5.48 (s, 2H); 7.18 (s, 1H); 7.19 (dd, 1H); 7.26 (t, 1H); 7.31 (m, 3H); 7.52 (m, 2H); 7.63-7.71 (m, 4H); 7.80 (d, 1H); 8.12 (d, 1H); 8.15 (d, 1H).

9H 3-Fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid

Following the process described in example 1 (point G), starting from 3-fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile, the title compound was prepared as a yellow solid with melting point 161-162°C which was purified by crystallization in methanol (75% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.93 (t, 2H); 3.71 (t, 2H); 4.61 (s, 2H); 5.49 (s, 2H); 7.23 (d, 1H); 7.30 (dd, 1H), 7.39 (d, 1H); 7.49 (t, 1H); 7.60-7.65 (m, 3H); 7.71-7.86 (sc, 5H); 8.01 (d, 1H), 8.06 (d, 1H); 8.43 (d, 1H).

Example 10: 3-Methoxy-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid

10A 5-Chloro-2-methylphenol

A suspension of 5-chloro-2-methylaniline (5 g, 35.3 mmol) in water (18 ml) was added in succession at 0°C with concentrated sulfuric acid (6.3 ml), ice (16 g) and sodium nitrite (2.84 g, 41.5 mmol) dissolved in water (8 ml), stirring at 0°C for 5 min. After that, the resulting solution was slowly poured onto a hot mixture of sodium sulfate (13.2 g), concentrated sulfuric acid (9.5 ml) and water (10 ml). The resulting mixture was left under stirring at 135°C for 3 h., then cooled at room temperature and extracted with ethyl ether (3x50 ml); the organic phase was washed with a 5% sodium thiosulfate solution, dried and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography eluting with mixtures of petroleum ether:ethyl ether of increasing polarity, thereby obtaining 2.63 g of the title compound (52% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.17 (s, 3H); 6.75 (d, 1H); 6.81 (dd, 1H); 6.97 (d, 1H); 12.55 (s, 1H).

10B 5-Chloro-2-methyl-1-methoxybenzene

5.23 M sodium methoxide in methanol (2.80 ml, 14.5 mmol) was added to a solution of 5-chloro-2-methylphenol (1.73 g, 12.1 mmol) in methanol (40 ml), stirring at room temperature for 5 min. After that, methyl iodide (2.3 ml, 36.4 mmol) was added, stirring at the solvent reflux for 1 h. Subsequently, the reaction mixture was distilled under normal pressure and the distillate was partitioned on a mixture of water:petroleum ether, 1:1 (100 ml total). The aqueous phase was extracted with pe-

troleum ether (3x50 ml), the combined organic phases were dried and the solvent was cold evaporated under reduced pressure, thereby obtaining 1.70 g of the title compound as a colourless oil (90% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.17 (s, 3H); 3.81 (s, 3H); 6.79-6.85 (m, 2H); 7.03 (d, 1H).

10C 4-Chloro-2-methoxybenzyl bromide

Following the process described in example 9 (point A), starting from 5-chloro-2-methyl-1-methoxybenzene, the title compound was prepared which was purified by flash chromatography through a silica gel column eluting with petroleum ether (60% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.82 (s, 3H); 4.46 (s, 2H); 6.81-6.87 (m, 2H); 7.19 (d, 1H).

10D 4-Chloro-2-methoxyphenylacetonitrile

Following the process described in example 9 (point B), starting from 4-chloro-2-methoxybenzyl bromide, the title compound was prepared (89% yield).

1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.53 (s, 2H); 3.75 (s, 3H); 6.78 (d, 1H); 6.84 (dd, 1H); 7.15 (d, 1H).

10E Methyl 4-chloro-2-methoxyacetate

Following successively the processs described in example 9 (points C and D), starting from 4-chloro-2-methoxyphenylacetonitrile, the title compound was prepared (90% total yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.55 (s, 2H); 3.64 (s, 3H); 3.74 (s, 3H); 6.83 (d, 1H); 6.85 (dd, 1H); 7.06 (d, 1H).

10F 2-(4-Chloro-2-methoxyphenyl)ethanol

Following the process described in example 1 (point C), starting from methyl 4-chloro-2-methoxyphenylace-

tate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with dicloromethane (71% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.79 (t, 2H); 3.70 (t, 2H); 3.73 (s, 3H); 6.79 (s, 1H); 6.81 (dd, 1H); 7.03 (d, 1H).

10G 4-(2-Hydroxyethyl)-3-methoxybenzonitrile

Following the process described in example 6 (point H), starting from 2-(4-chloro-2-methoxyphenyl)ethanol, the title compound was prepared which was purified by chromatography through a silica gel column eluting with dicloromethane (45% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.93 (t, 2H); 3.84 (t, 2H); 3.86 (s, 3H); 7.07 (d, 1H); 7.21 (dd, 1H); 7.27 (d, 1H).

10H 3-Methoxy-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile

Following the process described in example 6 (point I), starting from 7-(2-quinolinylmethyloxy)-2-naphthylmethyl methanesulfonate and 4-(2-hydroxyethyl)-3-methoxybenzonitrile, the title compound was prepared (41% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.97 (t, 2H); 3.67 (t, 2H); 3.74 (s, 3H); 4.61 (s, 2H); 5.52 (s, 2H); 7.00 (s, 1H); 7.16-7.31 (sc, 5H); 7.54-7.58 (m, 2H); 7.70-7.77 (m, 4H); 7.80 (d, 1H); 8.13 (d, 1H); 8.20 (d, 1H).

10H 3-Methoxy-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid

Following the process described in example 1 (point G), starting from 3-methoxy-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile, the title

compound was prepared as a white solid with melting point 180-181°C, which was purified by crystallization from dicloromethane and methanol mixtures and recrystallized in methanol (75% yield).

^1H N.M.R. (300 MHz, DMSO) δ ppm: 2.93 (t, 2H); 3.66 (t, 2H); 3.80 (s, 3H); 4.61 (s, 2H); 5.50 (s, 2H); 7.26 (dd, 1H); 7.30-7.34 (m, 2H); 7.44 (d, 1H); 7.46 (s, 1H); 7.50 (dd, 1H); 7.61-7.67 (m, 2H); 7.75 (d, 1H); 7.79-7.86 (sc, 3H); 8.01 (d, 1H), 8.06 (d, 1H); 8.44 (d, 1H).

Example 11: 3-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzoic acid

11A 3-(2-Hydroxyethyl)benzonitrile

Following the process described in example 6 (point H), starting from 2-(3-bromophenyl)ethanol, the title compound was prepared which was purified by chromatography through a silica gel column eluting with dicloromethane (74% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.54 (s broad, 1H); 2.87 (t, 2H); 3.84 (t, 2H); 7.38-7.53 (sc, 4H).

11B 3-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile

Following the process described in example 6 (point I), starting from methanesulfonate of 7-(2-quinolinylmethyloxy)-2-naphthylmethyl and of the 3-(2-hydroxyethyl)benzonitrile, the title compound was prepared (43% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.88 (t, 2H); 3.64 (t, 2H); 4.57 (s, 2H); 5.48 (s, 2H); 7.19 (s, 1H); 7.21 (dd, 1H); 7.29 (t, 2H); 7.38-7.51 (sc, 5H); 7.66-7.79 (sc, 5H), 8.10 (d, 1H); 8.12 (d, 1H).

11C 3-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyl-oxilethyl]benzoic acid

Following the process described in example 1 (point G), starting from 3-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]ethyl]benzonitrile, the title compound was prepared as a yellow solid with melting point 59-60°C, which was purified by crystallization in dichloromethane and methanol mixtures and recrystallized in methanol (58% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.90 (t, 2H); 3.65 (t, 2H); 4.56 (s, 2H); 5.45 (s, 2H); 7.20 (dd, 1H); 7.25 (dd, 1H), 7.33 (s, 1H); 7.36 (d, 1H); 7.47 (d, 1H); 7.56 (s, 1H); 7.58 (t, 1H); 7.69 (d, 1H); 7.71-7.83 (sc, 5H); 7.96 (d, 1H), 8.02 (d, 1H); 8.39 (d, 1H).

Example 12: 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthyl-methylthiolethyl]benzoic acid

12A S-2-(4-Cyanophenyl)ethyl thioacetate

Diethyl azodicarboxylate (1.07 ml, 6.8 mmol) was added at 0°C to a solution of triphenylphosphin (1.82 g, 6.8 mmol) in anhydrous tetrahydrofuran (20 ml), stirring at 0°C for 30 min. A solution of 4-(2-hydroxyethyl)benzonitrile (0.5 g, 3.4 mmol) and thioacetic acid (0.506 ml, 6.8 mmol) dissolved in tetrahydrofuran (5 ml) was added to the resulting suspension, stirring at room temperature for 24 h. Subsequently, the solvents were evaporated off under reduced pressure and the resulting residue was purified by chromatography through a silica gel column, eluting with petroleum ether:dicloromethane, 6:4, thereby obtaining 0.626 g of the title compound (90% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H); 2.86 (t,

2H); 3.05 (t, 2H); 7.27 (d, 2H); 7.52 (d, 2H).

12B 4-(2-Mercaptoethyl)benzonitrile

Following the process described in example 4 (point A), starting from S-2-(4-cyanophenyl)ethyl thioacetate, the title compound was prepared (73% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.79 (t, 2H); 2.96 (t, 2H); 7.29 (d, 2H); 7.56 (d, 2H).

12C 4-[2-[7-(2-Quinolinylmethyloxy)-2-naphthylmethyl-thio]ethyl]benzonitrile

Cesium carbonate (1.658 g, 5.0 mmol) was added to a solution of 4-(2-mercaptoethyl)benzonitrile (0.441 g, 2.48 mmol) in tetrahydrofuran (30 ml), stirring at room temperature for 15 min. After that, 7-(2-quinolinylmethyloxy)-2-naphthylmethyl methanesulfonate (1.0 g, 2.48 mmol) dissolved in the minimum amount of tetrahydrofuran was added, stirring at room temperature for 24 h. Subsequently the reaction mixture was filtered and the filtrate was evaporated to dryness. The resulting residue was purified by chromatography through a silica gel column eluting with dicloromethane, thereby obtaining 0.741 g of the title compound (65% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.56 (t, 2H); 2.77 (t, 2H); 3.74 (s, 2H); 5.46 (s, 2H); 7.04 (d, 2H); 7.16 (s, 1H); 7.22-7.26 (m, 2H); 7.47-7.28 (m, 2H); 7.40 (d, 1H); 7.49 (m, 2H); 7.63-7.74 (sc, 4H); 8.10 (d, 2H).

12D 4-[2[7-(2-Quinolinylmethyloxy)-2-naphthylmethyl-thio]ethyl]benzoic acid

Following the process described in example 1 (point G), starting from 4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethylthio]ethyl]benzonitrile, the title compound was prepared as a white solid with melting point

158-160°C which was purified by crystallization in methanol (60% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.64 (t, 2H); 2.87 (t, 2H); 3.89 (s, 2H); 5.50 (s, 2H); 7.29 (d, 2H); 7.30 (d, 1H), 7.34 (d, 1H); 4.41 (d, 1H); 7.63 (t, 1H); 7.68 (s, 1H); 7.74 (d, 1H); 7.78-7.83 (sc, 3H); 7.84 (d, 2H); 8.00 (d, 1H), 8.06 (d, 1H); 8.43 (d, 1H).

Example 13: 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoic acid

13A Methyl 4-cyanomethylbenzoate

Methyl 4-chloromethylbenzoate (8 g, 43.3 mmol) dissolved in ethanol (6 ml) was added to a solution of sodium cyanide (2.5 g, 51.0 mmol) in water (3 ml) leaving at 100°C for 3 h. The the mixture was cooled at room temperature, and ethyl ether (30 ml) and NaCl saturated solution (10 ml) were added thereto. The two phases were separated and the aqueous one was extracted with ethyl ether (3x25 ml). The ether extracts were dried and the solvent was evaporated off, to obtain a crude which was purified by flash chromatography through a silica gel column, eluting with petroleum ether:ethyl acetate, 3:2, thereby obtaining 6.1 g of the title compound as a yellowish oil (80 % yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.85 (s, 2H); 3.95 (s, 2H); 7.44 (d, 2H); 8.07 (d, 2H).

13B Methyl 4-(2-aminoethyl)benzoate

2.27 g of 10% palladium on carbon were added to a solution of methyl 4-cyanomethylbenzoate (6.10 g, 34.9 mmol) in methanol (400 ml) and HCl concentrated (20 ml), stirring at room temperature for 4 days, under hydrogen atmosphere. After that, the mixture was filt red and the

filtrate was evaporated to dryness to obtain a crude which was redissolved in hot methanol, thereby crystallizing 6.78 g of the title compound hydrochloride as a yellowish solid with melting point >360°C (90 % yield).

^1H N.M.R. (300 MHz, CD_3OD) δ ppm: 3.07 (t, 2H); 3.32 (t, 2H); 3.92 (s, 3H); 7.44 (d, 2H); 8.03 (d, 2H).

13C Sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate

Following the process described in example 1 (point A), starting from sodium 7-hydroxynaphthyl-2-sulfonate and 2-chloromethylquinoline, the title compound was prepared (75% yield).

^1H N.M.R. (300 MHz, DMSO) δ ppm: 5.50 (s, 2H); 7.34 (dd, 1H); 7.56-7.66 (m, 3H); 7.76-7.83 (m, 3H); 7.88 (d, 1H); 8.01 (d, 1H); 8.06 (d, 1H); 8.07 (s, 1H); 8.44 (d, 1H).

13D Methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylaminolethyl]benzoate

A mixture of phosphorous pentachloride (1.59 g, 7.64 mmol) and carbon tetrachloride (30 ml) was added to a solution of sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate (1.42 g, 3.82 mmol), stirring under reflux for 4 h. Subsequently the solvent was evaporated off and the residue was washed repeatedly with water. The washed solid was dried under reduced pressure over phosphorous pentoxide for 18 h. After that, a mixture consisting of the solid obtained above, methyl 4-(2-aminoethyl)benzoate hydrochloride (0.906 g, 4.20 mmol) and chloroform (100 ml) was added with triethylamine (2.13 ml, 15.3 mmol), stirring at reflux for 18 h. Subsequently the mixture was evaporated to dryness and the resulting residue was chromatographed through a silica gel column eluting with mixtures of n-hexane:chloroform of

increasing polarity, thereby obtaining 1.363 g of the title compound (67% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3/CD_3OD$ mixtures) δ ppm: 2.80 (t, 2H); 3.22 (t, 2H); 3.86 (s, 3H); 5.47 (s, 2H); 7.11 (d, 2H); 7.34 (s, 1H); 7.43 (dd, 1H); 7.56 (dt, 1H); 7.63 (dd, 1H); 7.70 (d, 1H); 7.75 (dt, 1H); 7.80-7.85 (m, 5H), 8.09 (d, 1H); 8.22 (d, 1H); 8.23 (d, 1H).

13E 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoate, the title compound was prepared as a white solid with melting point 213.4°-214.8°C (87% yield).

^{1}H N.M.R. (300 MHz, mixtures $CDCl_3/CD_3OD$) δ ppm: 2.73 (t, 2H); 3.09 (t, 2H); 5.45 (s, 2H); 7.06 (d, 2H); 7.40 (dd, 1H); 7.44 (d, 1H); 7.57 (dt, 1H); 7.68 (dd, 1H); 7.72 (d, 1H); 7.76 (dt, 1H); 7.80-7.90 (m, 5H), 8.05 (d, 1H); 8.26 (d, 1H); 8.31 (d, 1H).

Example 14: N-Methyl-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]benzoic acid

14A Methyl N-methyl-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]benzoate

A dispersion of sodium hydride (19 mg, 0.47 mmol) in 60% mineral was washed by decantation with anhydrous hexane and, subsequently, resuspended in dry N,N-dimethylformamide (10 ml). The resulting suspension was added at 0°C and under inert atmosphere with a solution of methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]ethyl]benzoate (0.250 mg, 0.47 mmol) in benzene (10 ml), stirring at room temperature for 4 h.

After that, methyl iodide (0.15 ml, 0.47 mmol) was added, stirring at room temperature for 18 h. After this time, water (50 ml) was added and the mixture was extracted with ethyl acetate (4x50 ml). The organic phase was dried and the solvent was evaporated off, to obtain a crude which was purified by chromatography through a silica gel column, eluting with mixtures of petroleum ether:chloroform of increasing polarity, thereby obtaining 50 mg of the title compound (20% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.69 (s, 2H); 2.81 (t, 2H); 3.24 (t, 2H); 3.81 (s, 3H); 5.42 (s, 2H); 7.15 (d, 2H); 7.24 (d, 1H); 7.36 (dd, 1H); 7.47 (dt, 1H); 7.49 (d, 1H); 7.59 (d, 1H); 7.67 (dt, 1H); 7.72-7.78 (m, 3H), 7.834 (d, 2H); 8.03 (d, 1H); 8.22 (s broad, 1H); 8.12 (d, 1H).

14B N-Methyl-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl N-methyl-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoate, the title compound was obtained as a white solid with melting point 213.6°-215.0°C (87% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.74 (s, 3H); 2.88 (t, 2H); 3.29 (t, 2H); 5.53 (s, 2H); 7.36 (d, 2H); 7.53 (dd, 1H); 7.58-7.68 (m, 2H); 7.72-7.84 (m, 3H); 7.86 (d, 2H); 8.00-8.10 (m, 4H); 8.32 (s, 1H); 8.45 (d, 1H).

Example 15: 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolmethyl]benzoic acid

15A Methyl 4-cyanobenzoate

Following the process described in example 4 (point A), starting from 4-cyanobenzoic acid, the title com-

pound was prepared as an yellowish oil (93% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 4.11 (s, 3H); 7.89 (d, 2H); 8.28 (d, 2H).

15B Methyl 4-aminomethylbenzoate

Following the process described in example 13 (point B), starting from methyl 4-cyanobenzoate and reacting for 4 h, the title compound was prepared as semi-solid oil (87% yield).

^{1}H N.M.R. (300 MHz, CD_3OD) δ ppm: 3.91 (s, 3H); 4.21 (s, 2H); 7.59 (d, 2H); 8.07 (d, 2H).

15C Methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]methyl]benzoate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-aminomethylbenzoate, the title compound was prepared which was purified by digestion with methanol (29% yield).

^{1}H N.M.R. (300 MHz, mixtures $CDCl_3/CD_3OD$) δ ppm: 3.86 (s, 3H); 4.18 (s, 2H); 5.49 (s, 2H); 7.11 (d, 2H); 7.34 (s, 1H); 7.44 (dd, 1H); 7.56 (dt, 1H); 7.63 (dd, 1H); 7.70 (d, 1H); 7.75 (dt, 1H); 7.80-7.85 (m, 5H), 8.11 (d, 1H); 8.21 (d, 1H); 8.22 (d, 1H).

15D 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]methyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]methyl]benzoate, the title compound was prepared as a white solid with melting point 223.1°-224.9°C (98% yield).

^{1}H N.M.R. (300 MHz, mixtures DMSO) δ ppm: 4.08 (d, 2H); 5.55 (s, 2H); 7.36 (d, 2H); 7.51 (dd, 1H); 7.62-7.70 (m,

3H); 7.77-7.85 (m, 4H); 7.99-8.10 (m, 4H); 8.28 (s broad, 1H); 8.40 (t, 1H); 8.48 (d, 1H).

Example 16: 3-Fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]benzoic acid

16A Methyl 4-(bromomethyl)-3-fluorobenzoate

Following the process described in example 9 (point A), starting from methyl 3-fluoro-4-methylbenzoate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with petroleum ether:ethyl ether, 95:5 (65% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.90 (s, 3H); 4.50 (s, 2H); 7.42 (t, 1H); 7.68 (d, 1H); 7.78 (d, 1H).

16B Methyl 4-(cyanomethyl)-3-fluorobenzoate

Following the process described in example 9 (point B), starting from methyl 4-(bromomethyl)-3-fluorobenzoate, the title compound was prepared (93% yield).

1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.82 (s, 2H); 3.92 (s, 3H); 7.53 (t, 1H); 7.71 (dd, 1H); 7.84 (dd, 1H).

16C Methyl 4-(2-aminoethyl)-3-fluorobenzoate

0.266 g of 10% palladium on carbon was added to a solution of methyl 4-(cyanomethyl)-3-fluorobenzoate (0.515 g, 2.67 mmol) in methanol (50 ml) and concentrated HCl (1.6 ml), stirring at room temperature for 24 h, under hydrogen atmosphere. After that, the mixture was filtered and the filtrate was evaporated to dryness to obtain 0.607 g of the title compound as the hydrochloride (97% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.10 (t, 2H); 3.21 (t, 2H); 3.91 (s, 3H); 7.47 (t, 1H); 7.72 (d, 1H); 7.83 (d, 1H).

16D Methyl 3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-aminoethyl)-3-fluorobenzoate, the title compound was obtained which was purified by chromatography through a silica gel column, eluting with petroleum ether:chloroform 25:75 (70% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.83 (t, 2H); 3.28 (q, 2H); 3.87 (s, 3H); 5.01 (m broad, 1H); 5.48 (s, 2H); 7.11 (t, 1H); 7.26 (s, 1H); 7.28 (d, 1H); 7.42 (dd, 1H); 7.49 (d, 1H); 7.56 (t, 1H); 7.57-7.62 (m, 2H); 7.68 (d, 1H); 7.75 (t, 1H); 7.78-7.84 (m, 2H), 8.10 (d, 1H); 8.18 (s, 1H); 8.19 (d, 1H).

16E 3-Fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]benzoate, the title compound was prepared as a white solid with melting point 196-198°C which was purified by chromatography through a silica gel column, eluting with chloroform:methanol, 98:2 (87% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.78 (t, 2H); 3.04 (q, 2H); 5.53 (s, 2H); 7.35 (t, 1H); 7.51 (sc, 2H); 7.63 (m, 3H); 7.71 (s, 1H); 7.74-7.83 (m, 2H); 7.86 (t, 1H); 7.98-8.07 (m, 4H), 8.27 (s, 1H); 8.44 (d, 1H).

Example 17: 4-[1-Methyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylaminolethyl]benzoic acid

17A Methyl 4-(cyanomethyl)benzoate

Following the process described in example 9 (point B), starting from methyl 4-(bromomethyl)benzoate, the title compound was prepared (86% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.82 (s, 2H); 3.90 (s, 3H); 7.40 (d, 2H); 8.00 (d, 2H).

17B Methyl 4-(1-cyanoethyl)benzoate

A solution of 1.6M n-butyl lithium in hexane (3.14 ml, 5.03 mmol) was added to a solution of diisopropylamine (0.774 ml, 5.48 mmol) in anhydrous tetrahydrofuran (20 ml), under inert atmosphere and at -78°C, stirring at -78°C for 30 min. After that, methyl 4-(cyanomethyl)benzoate (0.80 g, 4.57 mmol) was added slowly at -78°C, stirring at this temperature for 30 min. Subsequently, hexamethylphosphoramide (HMPA) (0.784 ml, 4.48 mmol) and methyl iodide (0.285 ml, 4.57 mmol) were added in succession, keeping at -78°C with stirring under inert atmosphere for 4 h. After this time, the mixture was left to cool and water (10 ml) and 1M HCl (10 ml) were added immediately. The mixture was extracted with ethyl ether (4x50 ml), dried and the solvent was evaporated off, the residue was purified by flash chromatography through a silica gel column, eluting with mixtures of petroleum ether:ethyl ether of increasing polarity, thereby obtaining 0.434 g of the title compound (50% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.68 (d, 3H); 3.92 (s, 3H); 4.00 (q, 1H); 7.47 (d, 2H); 8.07 (d, 2H).

17C Methyl 4-(2-amino-1-methylethyl)benzoate

Following the process described in example 16 (point C), starting from methyl 4-(1-cyanoethyl)benzoate, the title compound was prepared as the hydrochloride (83% yield).

^{1}H N.M.R. (300 MHz, CD_3OD) δ ppm: 1.38 (d, 3H); 3.19 (m, 3H); 3.90 (s, 3H); 7.46 (d, 2H); 8.01 (d, 2H).

17D Methyl 4-[1-methyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylaminolethyl]benzoate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-amino-1-methylethyl)benzoate, the title compound was obtained which was purified by digestion in methanol (60% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.21 (d, 3H); 2.95 (m, 1H); 3.08 (m, 1H); 3.25 (m, 1H); 3.89 (s, 3H); 4.75 (m broad, 1H); 5.54 (s, 2H); 7.10 (d, 2H); 7.32 (s, 1H); 7.48 (dd, 1H); 7.59 (t, 2H); 7.72 (d, 1H); 7.84 (m, 6H); 8.18 (d, 1H); 8.19 (s, 1H); 8.24 (d, 1H).

17E 4-[1-Methyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylaminolethyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 4-[1-methyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylamino]ethyl]benzoate, the title compound was prepared as a white solid with melting point 186.5-187.3°C, which was purified by digestion in tetrahydrofuran and methanol (80% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 1.14 (d, 3H); 2.90 (m, 3H); 5.51 (s, 2H); 7.25 (d, 2H); 7.50 (dd, 1H); 7.62 (t, 2H); 7.70 (d, 1H); 7.32-7.81 (m, 4H); 7.96-8.02 (m, 3H); 8.04 (d, 1H); 8.23 (s, 1H); 8.43 (d, 1H).

Example 18: 4-[1,1-Dimethyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylaminolethyl]benzoic

18A: Methyl 4-(1-cyano-1-methylethyl)benzoate

Following the process described in example 14 (point A), starting from methyl 4-(cyanomethyl)benzoate, sodium hydride, methyl iodide (2 equivalents) and tetrahydrofuran, the title compound was prepared (88% yield). ^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.79 (s, 6H); 3.94 (s, 3H); 7.57 (d, 2H); 8.08 (d, 2H).

18B Methyl 4-(2-amino-1,1-dimethylethyl)benzoate

Following the process described in example 16 (point C), starting from methyl 4-(1-cyano-1-methylethyl)benzoate, the title compound was prepared as the hydrochloride (quantitative yield). ^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.51 (s, 6H); 3.14 (s broad, 3H); 3.90 (s, 3H); 7.49 (d, 2H); 8.02 (d, 2H).

18C Methyl 4-[1,1-dimethyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylaminolethyl]benzoate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-amino-1,1-dimethylethyl)benzoate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with chloroform (55% yield). ^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.30 (s, 6H); 3.11 (d, 2H); 3.85 (s, 3H); 4.75 (m broad, 1H); 5.47 (s, 2H); 7.21-7.27 (m, 3H); 7.45 (dd, 1H); 7.54 (t, 2H); 7.66 (d, 1H); 7.75 (t, 1H); 7.80 (m, 5H); 8.11 (d, 1H); 8.15 (s, 1H); 8.20 (d, 1H).

18D 4-[1,1-Dimethyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylaminolethyllbenzoic

Following the process described in example 3 (point E), starting from methyl 4-[1,1-dimethyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsulfonylamino]ethyl]benzoate, the title compound was prepared as a white solid with melting point 219-220°C which was purified by digestion methanol (50% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 1.23 (s, 6H); 2.90 (d, 2H); 5.52 (s, 2H); 7.40 (d, 2H); 7.48 (dd, 1H); 7.57-7.64 (m, 2H); 7.68 (s, 1H); 7.72-7.82 (m, 4H); 7.96-8.05 (m, 4H); 8.23 (s, 1H); 8.43 (d, 1H).

Example 19: 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyllsulfonylaminolpropyllbenzoic acid

19A Methyl 4-formylbenzoate

Following the process described in example 4 (point A), starting from 4-formylbenzoic, the title compound was prepared (quantitative yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.94 (s, 3H); 7.94 (d, 2H); 8.18 (d, 2H); 10.08 (s, 1H).

19B Methyl 4-(2-nitro-1-propenyl)benzoate

A mixture of methyl 4-formylbenzoate (4.82 g, 29.4 mmol), ammonium acetate (2.26 g, 29.4 mmol) and nitroethane (87 ml) was stirred at 110°C for 2.5 h. After this time, the solvent was evaporated off under reduced pressure and the resulting residue was partitioned in a mixture of dicloromethane:water, 1:1 (100 ml). The aqueous phase was extracted with dicloromethane (3x50 ml) and the combined organic extracts were dried and evaporated to dryness under reduced pressure. The resulting residue was purified by chromatography through

a silica gel column, eluting with hexane:chloroform, 1:1, thereby obtaining 5.39 g of the title compound (83% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.42 (s, 3H); 3.92 (s, 3H); 7.48 (d, 2H); 8.08 (s, 1H); 8.10 (d, 2H).

19C Methyl 4-(2-oxopropyl)benzoate

Glacial acetic acid (50 ml) was added to a mixture of methyl 4-(2-nitro-1-propenyl)benzoate (3.4 g, 15.4 mmol), powder iron (8.34 g, 0.149 mol), methanol (50 ml) and water (6.2 ml), stirring at reflux for 3 h. After that, the mixture was cooled and filtered over, washing with methanol. The filtrate was concentrated by evaporation under reduced pressure and extracted with dicloromethane (4x50 ml). The organic phase was dried and the solvent was evaporated off under reduced pressure, thereby obtaining 2.833 g of the title compound (95% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.15 (s, 3H); 3.71 (s, 2H); 3.88 (s, 3H); 7.23 (d, 2H); 7.97 (d, 2H).

19D Methyl 4-(2-aminopropyl)benzoate

Sodium borohydride (0.684 g, 10.9 mmol) was added to a solution of methyl 4-(2-oxopropyl)benzoate (2.10 g, 10.9 mmol) and ammonium acetate (8.40 g, 10.9 mmol) in methanol (45 ml), stirring at room temperature for 18 h. After that the solvent was evaporated off and the residue was partitioned in a mixture of dicloromethane:water, 1:1 (100 ml). The aqueous phase was alkalinized with 1N NaOH and extracted with dicloromethane (3x50 ml), then dried and the solvent was evaporated off under reduced pressure to obtain a residue which was purified by chromatography through a silica gel column

eluting with chloroform:methanol, 97:3, thereby obtaining 1,36 g of the title compound (64% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.02 (d, 3H); 1.91 (s broad, 2H); 2.52 (dd, 1H); 2.68 (dd, 1H); 3.80 (s, 3H); 7.16 (d, 2H); 7.87 (d, 2H).

19E Methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonilamino]propyl]benzoate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-aminopropyl)benzoate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with petroleum ether:chloroform, 2:8 (75% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.12 (d, 3H); 2.68 (d, 2H); 3.60 (m, 1H); 3.84 (s, 3H); 5.14 (d, 1H); 5.47 (s, 2H); 6.99 (d, 2H); 7.24 (s, 1H); 7.41 (dd, 1H); 7.50 (dd, 1H); 7.53 (t, 1H); 7.64 (d, 1H); 7.67-7.81 (sc, 6H); 8.11 (s, 1H); 8.12 (d, 1H); 8.18 (d, 1H).

19F 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-[[7-(2-quinolinylmethyloxy)2-naphthyl]sulfonylamino]propyl]benzoate, the title compound was prepared as a white solid with melting point 221-224°C which was purified by digestion in ethyl ether (85% yield)

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 0.91 (d, 3H); 2.68 (d, 2H); 3.48 (m, 1H); 5.54 (s, 2H); 7.17 (d, 2H); 7.48 (dd, 1H); 7.56 (dd, 1H); 7.63 (t, 1H); 7.69 (s, 1H); 7.71 (d, 2H); 7.78 (d, 1H); 7.79-7.84 (m, 2H); 7.94 (d, 1H); 7.96

(d, 1H); 8.02 (d, 1H); 8.08 (d, 1H); 8.23 (s, 1H); 8.46 (d, 1H).

Example 20: 5-[4-[2-[[7-(Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenyl]-1*H*-tetrazole

20A 4-(2-Nitro-1-propenyl)benzonitrile

Following the process described in example 19 (point B), starting from 4-formylbenzonitrile, the title compound was prepared (85% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.44 (s, 3H); 7.54 (d, 2H); 7.76 (d, 2H); 8.05 (s, 1H).

20B 4-(2-Oxopropyl)benzonitrile

Following the process described in example 19 (point C), starting from 4-(2-nitro-1-propenyl)benzonitrile, the title compound was prepared (87% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.22 (s, 3H); 3.80 (s, 2H); 7.31 (d, 2H); 7.63 (d, 2H).

20C 4-(2-Aminopropyl)benzonitrile

Following the process described in example 19 (point D), starting from 4-(2-oxopropyl)benzonitrile, the title compound was prepared (67% yield).

^{1}H N.M.R. (300 MHz, CD_3OD) δ ppm: 1.09 (d, 3H); 2.73 (dd, 2H); 3.17 (m, 1H); 7.39 (d, 2H); 7.64 (d, 2H).

20D 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzonitrile

Following the process described in example 13 (Point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and 4-(2-aminopropyl)-benzonitrile, the title compound was prepared which was purified by chromatography through a silica gel column eluting with chloroform (72% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.12 (d, 3H); 2.71 (t, 2H); 3.59 (m, 1H); 4.70 (d, 1H); 5.52 (s, 2H); 7.03 (d, 2H); 7.26 (t, 3H); 7.47 (m, 2H); 7.57 (t, 1H); 7.70-7.87 (sc, 5H); 8.13 (s, 1H); 8.13 (d, 1H); 8.22 (d, 1H).

20E 5-[4-[2-[[7-(Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenyl]-1*H*-tetrazole

Following the process described in example 2, starting from 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]propyl]benzonitrile, the title compound was prepared as a white solid with melting point 128-130°C which was purified by chromatography through a silica gel column eluting with chloroform:methanol, 96:4 (83% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 0.97 (d, 3H); 2.66 (m, 2H); 3.49 (m, 1H); 4.70 (d, 1H); 5.48 (s, 2H); 7.24 (d, 2H); 7.33 (dd, 1H); 7.50 (d, 1H); 7.60 (s, 1H); 7.63 (t, 1H); 7.69 (d, 2H); 7.69-7.87 (sc, 5H); 8.02 (d, 1H); 8.06 (d, 1H); 8.12 (s, 1H); 8.46 (d, 1H).

Example 21: 3-Fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid

21A Methyl 3-fluoro-4-formylbenzoate

Following the process described in example 4 (point A), starting from 3-fluoro-4-formylbenzoic acid, the title compound was prepared (quantitative yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.97 (s, 3H); 7.79 (d, 1H); 7.89 (m, 2H); 10.39 (s, 1H).

21B Methyl 3-fluoro-4-(2-nitro-1-propenyl)benzoate

Following the process described in example 19 (point B), starting from methyl 3-fluoro-4-formylbenzoate, the title compound was prepared (65% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.40 (s, 3H); 3.96 (s,

3H); 7.47 (t, 1H); 7.80 (dd, 1H); 7.91 (dd, 1H); 8.07 (s, 1H).

21C Methyl 3-fluoro-4-(2-oxopropyl)benzoate

Following the process described in example 19 (point C), starting from methyl 3-fluoro-4-(2-nitro-1-propenyl)benzoate, the title compound was prepared (90% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.21 (s, 3H); 3.81 (s, 2H); 3.89 (s, 3H); 7.24 (t, 1H); 7.68 (d, 1H); 7.76 (d, 1H).

21D Methyl 4-(2-aminopropyl)-3-fluorobenzoate

Following the process described in example 19 (point D), starting from methyl 3-fluoro-4-(2-oxo-propyl)benzoate, the title compound was prepared (76% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.13 (d, 3H); 1.87 (s broad, 2H); 2.68 (dd, 1H); 2.77 (dd, 1H); 3.23 (m, 1H); 7.28 (t, 1H); 7.69 (d, 1H); 7.77 (d, 1H).

21E Methyl 3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyl-oxy)-2-naphthylsulfonate and methyl 4-(2-aminopropyl)-3-fluorobenzoate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with petroleum ether:chloroform, 1:4 (65% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.21 (d, 3H); 2.70 (d, 2H); 3.66 (m, 1H); 3.84 (s, 3H); 4.79 (d, 1H); 5.50 (s, 2H); 6.99 (t, 1H); 7.23 (s, 1H); 7.25 (dd, 1H); 7.39 (d, 2H); 7.49 (dd, 1H); 7.56 (t, 1H); 7.67 (d, 1H); 7.72-

7.78 (sc, 3H); 7.83 (d, 1H); 8.05 (s, 1H); 8.13 (d, 1H); 8.21 (d, 1H).

21F 3-Fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoate, the title compound was prepared as a white solid with melting point 228-230°C which was purified by digestion in ethyl ether (77% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 0.94 (d, 3H); 2.68 (d, 2H); 3.48 (m, 1H); 5.54 (s, 2H); 7.28 (t, 1H); 7.35 (d, 1H); 7.46-7.54 (m, 3H); 7.67 (m, 2H); 7.77-7.95 (sc, 5H); 8.02 (d, 1H); 8.07 (d, 1H); 8.18 (s, 1H); 8.46 (d, 1H).

Example 22: 3-Methoxy-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid

22A Methyl 4-methyl-3-methoxybenzoate

Potassium carbonate (4.54 g, 32.9 mmol) and methyl iodide (3.07 ml, 49.3 mmol) were added in succession to a solution of 3-hydroxy-4-methylbenzoic acid (2.5 g, 16.4 mmol) in acetone (30 ml), stirring at reflux for 18 h. After that, the solution was filtered and the filtrate was washed with water (20 ml). The organic phase was dried and the solvent was evaporated off under reduced pressure, thereby obtaining 3.18 g of the title compound (quantitative yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.25 (s, 3H); 3.85 (s, 3H); 3.88 (s, 3H); 7.15 (d, 1H); 7.48 (s, 1H); 7.55 (d, 1H).

22B Methyl 4-(dibromomethyl)-3-methoxybenzoate

Following the process described in example 9 (point A), starting from methyl 4-methyl-3-methoxybenzoate and 2 equivalents of N-bromosuccinimide, the title compound was prepared (quantitative yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.91 (s, 3H); 3.92 (s, 3H); 7.11 (s, 1H); 7.48 (d, 1H); 7.67 (dd, 1H); 7.89 (d, 1H).

22C Methyl 4-formyl-3-methoxybenzoate

Water (3 ml) was added to a mixture of methyl 4-(dibromomethyl)-3-methoxybenzoate (1.80 g, 4.81 mmol) and calcium carbonate (1.64 g, 16.3 mmol), stirring at reflux for 2 h. After that, water (10 ml) and a 0.2N HCl solution (10 ml) were poured onto the cooled mixture which was extracted with ethyl ether (4x25 ml). The ether phase was dried and the solvent was evaporated under reduced pressure to obtain 0.86 g of the title compound (91% yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.94 (s, 3H); 3.98 (s, 3H); 7.61 (s, 1H); 7.62 (d, 1H); 7.81 (dd, 1H); 10.47 (s, 1H).

22D Methyl 3-methoxy-4-(2-nitro-1-propenyl)benzoate

Following the process described in example 19 (point B), starting from methyl 4-formyl-3-methoxybenzoate, the title compound was prepared (quantitative yield).

^1H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.37 (s, 3H); 3.93 (s, 3H); 3.94 (s, 3H); 7.34 (d, 1H); 7.60 (s, 1H); 7.68 (d, 1H); 8.20 (s, 1H).

22E Methyl 3-methoxy-4-(2-oxopropyl)benzoate

Following the process described in example 19

(point C), starting from methyl 3-methoxy-4-(2-nitro-1-propenyl)benzoate, the title compound was prepared (65% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.15 (s, 3H); 3.72 (s, 2H); 3.86 (s, 3H); 3.90 (s, 3H); 7.18 (d, 1H); 7.54 (d, 1H); 7.62 (dd, 1H).

22F Methyl 4-(2-aminopropyl)-3-methoxybenzoate

Following the process described in example 19 (point D), starting from methyl 3-methoxy-4-(2-oxopropyl)benzoate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with chloroform:methanol, 99:1 (85% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.11 (s, 3H); 1.92 (s broad, 2H); 2.63 (dd, 1H); 2.76 (dd, 1H); 3.22 (m, 1H); 3.86 (s, 3H); 3.90 (s, 3H); 7.19 (d, 1H); 7.51 (d, 1H); 7.58 (dd, 1H).

22G 3-Methoxy-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylaminolpropyl]benzoic acid

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-aminopropyl)-3-methoxybenzoate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with chloroform (64% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.22 (d, 3H); 2.54 (m, 2H); 3.41 (s, 3H); 3.60 (m, 1H); 3.78 (s, 3H); 5.38 (d, 1H); 5.42 (s, 2H); 6.79 (d, 1H); 6.87 (s, 1H); 7.12 (s, 1H); 7.13 (dd, 1H); 7.29-7.35 (m, 3H); 7.62-7.74 (sc, 5H); 7.94 (s, 1H); 8.07 (d, 1H); 8.11 (d, 1H).

22H 3-Methoxy-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoic acid

Following the process described in example 3 (point E), starting from methyl 3-methoxy-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]benzoate, the title compound was prepared as a white solid with melting point 186-187°C (94% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 0.95 (d, 3H); 2.57 (m, 2H); 3.48 (s, 3H); 3.51 (m, 1H); 5.56 (s, 2H); 7.10 (s, 1H); 7.12 (d, 1H); 7.36 (d, 1H); 7.50 (m, 2H); 7.64 (t, 1H); 7.69 (s, 1H); 7.77-7.84 (m, 3H); 7.85 (d, 1H); 7.94 (d, 1H); 8.02 (d, 1H); 8.07 (d, 1H); 8.20 (s, 1H); 8.46 (d, 1H).

Example 23: 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic

23A 4-(Cyanomethyl)phenylacetic acid

Following the process described in example 9 (point B), starting from 4-(bromomethyl)phenylacetic acid, the title compound was prepared (92% yield).

^{1}H N.M.R. (300 MHz, CD_3OD) δ ppm: 3.65 (s, 2H); 3.70 (s, 3H); 7.30 (s, 4H).

23B Methyl 4-(cyanomethyl)phenylacetate

Following the process described in example 4 (point A), starting from 4-(cyanomethyl)phenylacetic acid, the title compound was prepared (60% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.60 (s, 2H); 3.66 (s, 3H); 3.68 (s, 2H); 7.26 (s, 4H).

23C Methyl 4-(2-aminoethyl)phenylacetate

Following the process described in example 16 (point C), starting from methyl 4-(cyanomethyl)phenylacetate, the title compound was prepared as

the hydrochloride (85% yield).

^{1}H N.M.R. (300 MHz, CD_3OD) δ ppm: 3.00 (t, 2H); 3.21 (t, 2H); 3.69 (s, 2H); 3.71 (s, 3H); 7.30 (s, 4H).

23D Methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylaminolethyl]phenylacetate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-aminoethyl)-phenylacetate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with petroleum ether:chloroform 3:7 (55% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.85 (t, 2H); 3.35 (q, 2H); 3.67 (s, 2H); 3.80 (s, 3H); 5.32 (t broad, 1H); 5.61 (s, 2H); 7.13 (d, 2H); 7.24 (d, 2H); 7.45 (s, 1H); 7.56 (dd, 1H); 7.68 (t, 1H); 7.77 (dd, 1H); 7.81 (d, 1H); 7.87 (dt, 1H); 7.92-7.97 (m, 3H); 8.25 (d, 1H); 8.32 (d, 1H); 8.39 (s, 1H).

23E 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]phenylacetic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetate, the title compound was prepared as a white solid with melting point 217-219°C (92% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 2.68 (t, 2H); 2.99 (q, 2H); 3.19 (s, 2H); 5.54 (s, 2H); 7.07 (d, 2H); 7.12 (d, 2H); 7.53 (dd, 1H); 7.65 (t, 1H); 7.68 (s, 1H); 7.74-7.85 (m, 4H); 8.00-8.08 (m, 4H), 8.30 (s, 1H); 8.46 (d, 1H).

Example 24: 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenylacetic acid

24A 4-Formylphenylacetic acid

A mixture of 4-(bromomethyl)phenylacetic acid (4.14 g, 18.2 mmol), hexamethylenetetramine (3.06 g, 21.9 mmol), water (8 ml) and glacial acetic acid (8 ml) was refluxed with stirring for 2.5 h. After this time, 0.2 ml of concentrated HCl were added, stirring at the temperature of reflux for a further 15 minutes. Subsequently the mixture was left to cool, extracted with ethyl ether (4x25 ml) and dried, and the solvent was evaporated off to obtain 1.93 g of the title compound (88% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.78 (s, 2H); 7.45 (d, 2H); 7.86 (d, 2H); 9.99 (s, 1H).

24B Methyl 4-formylphenylacetate

Following the process described in example 4 (point A), starting from 4-formylphenylacetic acid, the title compound was prepared (96% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 3.66 (s, 2H); 3.70 (s, 3H); 7.43 (d, 2H); 7.79 (d, 2H); 9.94 (s, 1H).

24C Methyl 4-(2-nitro-1-propenyl)phenylacetate

Following the process described in example 19 (point B), starting from methyl 4-formylphenylacetate, the title compound was prepared (65% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.44 (s, 3H); 3.69 (s, 2H); 3.70 (s, 3H); 7.38 (s, 4H); 8.05 (s, 1H).

24D Methyl 4-(oxopropyl)phenylacetate

Following the process described in example 19 (point C), starting from methyl 4-(2-nitro-1-propenyl)phenylacetate, the title compound was prepared

(88% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 2.12 (s, 3H); 3.59 (s, 2H); 3.64 (s, 7H); 7.14 (d, 2H); 7.22 (d, 2H).

24E Methyl 4-(2-aminopropyl)phenylacetate

Following the process described in example 19 (point D), starting from methyl 4-(2-oxopropyl)phenylacetate, the title compound was prepared (62% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.09 (d, 3H); 1.99 (s broad, 2H); 2.50 (dd, 1H); 2.68 (dd, 1H); 3.12 (m, 1H); 3.58 (s, 2H); 3.65 (s, 3H); 7.13 (d, 2H); 7.19 (d, 2H).

24F Methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]propyl]phenylacetate

Following the process described in example 13 (Point D), starting from sodium 7-(2-quinolinylmethyloxy)-2-naphthylsulfonate and methyl 4-(2-aminopropyl)phenylacetate, the title compound was prepared which was purified by chromatography through a silica gel column eluting with petroleum ether:chloroform, 4:6 (55% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) δ ppm: 1.05 (d, 3H); 2.61 (d, 2H); 3.45 (s, 2H); 3.52 (m, 1H); 3.64 (s, 3H); 5.65 (d, 1H); 5.49 (s, 2H); 6.88 (d, 2H); 6.97 (d, 2H); 7.29 (d, 1H); 7.41 (dd, 1H); 7.48 (dd, 1H); 7.54 (t, 1H); 7.67 (d, 1H); 7.73-7.80 (sc, 4H); 8.10 (d, 1H); 8.17 (s, 1H); 8.18 (d, 1H).

24G 4-[2-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenylacetic acid

Following the process described in example 3 (point E), starting from methyl 4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenylacetate, the

title compound was prepared as a white solid with melting point 212-213°C (85% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 0.83 (d, 3H); 2.47 (dd, 1H); 2.58 (dd, 1H); 3.38 (m, 1H); 3.39 (s, 2H); 5.51 (s, 2H); 6.93 (d, 2H); 6.98 (d, 2H); 7.47 (dd, 1H); 7.52 (dd, 1H); 7.61 (dt, 1H); 7.69-7.81 (sc, 4H); 7.93-8.00 (sc, 3H); 8.03 (d, 1H); 8.24 (s, 1H); 8.43 (d, 1H).

Example 25: 4-[1-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]phenylacetic acid

25A Methyl 4-acetylphenylacetate and methyl 2-acetylphenylacetate

Aluminium trichloride (19.58 g, 0.145 mol) was added to a mixture of methyl phenylacetate (10.0 g, 0.066 mol) and acetyl chloride (9.42 ml, 0.132 mol). The mixture was kept under stirring at 90°C for 4 h, then it was left to cool, added slowly with water (30 ml) and extracted with ethyl ether (4x30 ml). The combined ether extracts were dried and the solvent was evaporated off under reduced pressure. The resulting oily residue was distilled under high vacuum (0.1 torr) to obtain 10.1 g of a distilled oil which was a mixture 1:1 of the two title isomers (84% total yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) of the isomer *para* δ ppm: 2.62 (s, 3H); 3.72 (s, 5H); 7.41 (d, 2H); 7.95 (d, 2H).

^{1}H N.M.R. (300 MHz, $CDCl_3$) of the isomer *ortho* δ ppm: 2.62 (s, 3H); 3.72 (s, 5H); 7.46 (t, 1H); 7.52 (t, 1H); 7.90 (m, 2H).

25B Methyl 4-(1-aminoethyl)phenylacetate and methyl 2-(1-aminoethyl)phenylacetate

Following the process described in example 19 (point D), starting from the isomer mixture obtained in

point A of example 25, a 1:1 mixture of the title isomers was obtained (67% total yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) of the isomer *para* δ ppm: 1.33 (d, 3H); 1.57 (s broad, 2H); 3.58 (s, 2H); 3.64 (s, 3H); 4.05 (q, 1H); 7.22 (s, 4H).

^{1}H N.M.R. (300 MHz, $CDCl_3$) of the isomer *orto* δ ppm: 1.32 (d, 3H); 1.57 (s broad, 2H); 3.56 (s, 2H); 3.63 (s, 3H); 4.05 (q, 1H); 7.10-7.24 (m, 4H).

25C Methyl 4-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonyla-minolethyl]phenylacetate and methyl 2-[1-[[7-[2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]-phenylacetate

Following the process described in example 13 (point D), starting from sodium 7-(2-quinolinylmethyl-oxy)-2-naphthylsulfonate and the isomer mixture obtained in point B of example 25, a mixture of the title isomers was prepared. The isomer methyl 4-[1-[[7-(2-quino-linylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenyl-acetate was separated from the mixture by crystallization with petroleum ether:chloroform mixtures (30% yield), whereas the isomer methyl 2-[1-[[7-(2-qui-nolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenyl-acetate was recovered from crystallization mother liquors once separated the isomer *para* (36% yield).

^{1}H N.M.R. (300 MHz, $CDCl_3$) of the isomer *para* δ ppm: 1.41 (d, 3H); 3.41 (s, 2H); 3.66 (s, 3H); 4.50 (m, 1H); 5.29 (d, 1H); 5.53 (s, 2H); 6.98 (d, 2H); 7.05 (d, 2H); 7.27 (d, 1H); 7.44 (dd, 1H); 7.58 (dd, 1H); 7.60 (t, 1H); 7.72 (d, 1H); 7.76-7.88 (sc, 4H); 8.13 (s, 1H); 8.18 (d, 1H); 8.24 (d, 1H).

^{1}H N.M.R. (300 MHz, $CDCl_3$) of the isomer *ortho* δ ppm:

1.38 (d, 3H); 3.25 (s, 2H); 3.60 (s, 3H); 4.50 (m, 1H); 5.48 (s, 2H); 5.79 (d, 1H); 6.85-7.05 (sc, 4H); 7.20 (d, 1H); 7.38 (dd, 1H); 7.53 (t, 1H); 7.58 (dd, 1H); 7.74 (d, 1H); 7.78-7.85 (sc, 4H); 8.05 (s, 1H); 8.13 (d, 1H); 8.18 (d, 1H).

25D 4-[1-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]phenylacetic acid

Following the process described in example 3 (point E), starting from methyl 4-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetate, the title compound was prepared as a white solid with melting point 204-206°C which was purified by crystallization in methanol (92% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 1.16 (d, 3H); 3.17 (d, 2H); 4.36 (m, 1H); 5.53 (s, 2H); 6.98 (d, 2H); 7.11 (d, 2H); 7.48 (dd, 1H); 7.59 (dt, 1H); 7.61-7.66 (sc, 2H); 7.75-7.83 (sc, 2H); 7.94-8.08 (sc, 4H); 8.15 (s, 1H); 8.22 (d, 1H); 8.46 (d, 1H).

Example 26: 2-[1-[[7-(2-Quinolinylmethyloxy)-2-naphthyl]sulfonylaminolethyl]phenylacetic acid

Following the process described in example 3 (point E), starting from methyl 2-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetate, the title compound was prepared as a white solid with melting point 185-186°C which was purified by crystallization in methanol (92% yield).

^{1}H N.M.R. (300 MHz, DMSO) δ ppm: 1.17 (d, 3H); 3.17 (d, 2H); 4.38 (m, 1H); 5.52 (s, 2H); 6.90-7.15 (sc, 4H); 7.48 (dd, 1H); 7.59 (dt, 1H); 7.61-7.66 (sc, 2H); 7.75-7.83 (sc, 2H); 7.94-8.08 (sc, 4H); 8.12 (s, 1H); 8.25 (d, 1H); 8.46 (d, 1H).

Biological activity tests

The antagonistic activity on LTD_4 of the compounds of the present invention is determined by means of an inhibition test of the $[^3H]$-LTD_4 receptor binding in guinea-pig lung membranes, and a test of inhibition of LTD_4-induced contractions in the myenteric plexus of guinea-pig isolated ileum.

$[^3H]$-LTD_4 receptor binding inhibition test in guinea-pig lung membranes

Guinea pig lung membranes, containing the LTD_4 receptors, are purified following the method described by Mong et. al. (Mong et al., Prostaglandins, 28, 805 (1984)). These purified membranes (150 µg/ml) are added to an incubation mixture containing 10 mM of PIPES buffer (piperazin-N,N'-bis(2-ethanesulfonic acid) (pH 7.4), 10 mM of $CaCl_2$, 10 mM of 5 $MgCl_2$, 2 mM of cysteine, 2 mM of glycine, 0.5 nM of $[^3H]$-LTD_4 (4700-6400 GBq/mmol) and different concentrations of the product under test in a final volume of 310 µl. The reaction mixture is incubated for 30 minutes at 25°C.

The radioligand bound to the membranes is separated from the free one by dilution with 4 ml washing buffer (10 mM Tris-HCl (pH 7.4) and 100 mM NaCl) at 0°C and filtration with Whatman GF/B filters, by means of a Brandel Cell Harvester. The filters are washed 4 times with a total volume of 16 ml of washing buffer at 0°C. The radioactivity present in the filters is determined by liquid scintillation.

The specific binding is defined as the difference between the total binding of $[^3H]$-LTD_4 and the non-specific binding determined in the presence of 1 µM

LTD_4. The data obtained in the competition tests are analyzed by a computational program, which determines the inhibition constant of each compound (K_i) by means of the Cheng-Prusoff equation (Cheng et al., Biochem. Pharmacol., 22, 3094 (1973)).

$K_i = IC_{50} / (1 + [L] / K_d)$

wherein IC_{50} is the concentration of compound which displaces a 50% of the bound radioligand, [L] is the concentration of $[^3H]LTD_4$ free in the test and K_d is the dissociation constant of the LTD_4 obtained in an independent way by means of Scatchard analysis.

The selected compounds of general formula I show in the described test, inhibition of the receptor binding Ki ranging between 1000 and 0.1 nM.

Inhibition test of the contractions induced by LTD_4 in the myenteric plexus of guinea-pig isolated ileum.

The antagonistic activity of the compounds of the present invention in the isolated organ was evaluated as its ability to inhibit the contraction caused by LTD_4 in the myenteric plexus of the ileum of Dunkin Hartley male albino guinea-pig, weighing 300-350 g (Cristol J.P. and Sirois P. Res. Commun. Chem. Pathol., 59, 423 (1988)).

The smooth muscle of guinea-pig ileum exhibits sensitivity to leukotrienes and especially to LTD_4, which acts as primary mediator in the inflammatory and allergic response (Carnathan G.W. et al. Agents Actions, 20, 124 (1987)).

The myenteric plexus is extracted from a 2-3 cm segment of the terminal portion of the guinea-pig ileum, previously sacrificed by cervical dislocation. The plexus is put, at a tension of 0.5 g, in a 5 ml organ

bath, containing a solution of Tyrode (137 mM NaCl, 2.7 mM KCl, 1.4 mM $CaCl_2$, 0.4 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, 0.8 mM $MgSO_4$, 5.5 mM glucose), saturated with carbogen gas (95% O_2-5% CO_2) at 37°C. The solution also contains indomethacin (3.3 μM) and atropine (0.4 μM) to remove the action of the intrinsic prostaglandins and the cholinergic responses.

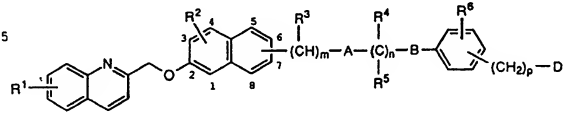
After a 45 minute stabilization period a maximum isotonic response is obtained (100% contractile response) adding to the bath chamber the LTD_4 agonist (3 nM). This process is repeated until the same contraction response is obtained twice. The isometric measures are made in an isotonic transducer.

After stabilization is restored, the product under test is incubated at different concentrations (dissolved in 0.1% final concentration DMSO) for 2.5 minutes, and after that the contraction with LTD_4 is induced again. The antagonistic activity is expressed as IC_{50}, the concentration of compound which reduces by 50% the maximum contraction.

The selected compounds of general formula I show in the described test inhibition of the contractions in the myenteric plexus of ileum IC_{50} ranging between 100 and 0.1 nM.

CLAIMS

1. A compound of formula I,



I

wherein:

the substituent containing A is bound to the 6- or 7-position of the 2-naphthol system;

$-R^1$, R^2, R^6 are independently hydrogen, fluorine, chlorine, bromine, $-OCH_3$ or (C_1-C_4)-alkyl;

$-R^3$ is hydrogen or methyl;

$-R^4$, R^5 are independently hydrogen, -OH, $-NH_2$, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkylamino, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkylcarbonylamino, (C_1-C_4)-alkoxycarbonylalkyl, carbamoyl, carbamoylalkyl, N,N-dialkylcarbamoylalkyl;

-A- is a diradical -O-, -S-, $-SO_2-$, -SO-, $-SO_2NR^7-$ or $-NR^7SO_2-$ wherein R^7 is hydrogen or methyl;

-B is a sulfur or oxygen atom or a $-SO_2-$ or -SO- group or a single bond;

-D is a 5-tetrazolyl or $-COOR^8$ group, wherein R^8 is hydrogen, a (C_1-C_4)-alkyl or a phenylalkyl group of less than 10 carbon atoms;

m is an integer from 0 to 4;

n and p are integers from 0 to 6, with the proviso that n + p is less or equal to 6.

2. A compound according to claim 1 wherein R^2 is

hydrogen, D is a 5-tetrazolyl or $COOR^8$ group, and R^8 is hydrogen, methyl, ethyl or benzyl.

3. A compound according to any one of claims 1 or 2 wherein R^1 is hydrogen or chlorine, and -A- is -O-, -S-, $-SO_2NR^7-$ or $-NR^7SO_2-$, wherein R^7 is hydrogen or methyl.

4. A compound according to any one of claims 1 a 3 wherein the substituent containing A is bound to the 7-position of the 2-naphthol ring.

5. A compound according to claim 4 wherein m is 0 and -A- is -O- or -S-.

6. A compound according to claim 4 wherein m is 1 and -A- is -O- or -S-.

7. A compound according to claim 4 wherein m is 0 and -A- is $-SO_2NR^7-$, wherein R^7 is hydrogen or methyl.

8. A compound according to claim 4 wherein n and p are integers from 0 to 4.

9. A compound according to claim 1 selected from the following ones:

4-[3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyl]-benzoic acid;

5-[4-[3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]propyl]-phenyl]-1H-tetrazole;

4-[3-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]butyl]-benzoic acid;

4-[2-[7-(2-quinolinylmethyloxy)-2-naphthyloxy]ethoxy]-benzoic acid;

4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]-ethyl]benzoic acid;

4-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxymethyl]-benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylami-

no]ethyl]benzoic acid;

N-methyl-4-[2-[[7-(2-quinolinyl-methyloxy)-2-naphthyl]-sulfonylamino]ethyl]benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonyl-amino]methyl]benzoic acid;

4-[2-hydroxy-3-[7-(2-quinolinylmethyloxy)-2-naphthyl-oxy]propyloxy]benzoic acid;

5-[4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]-ethyl]phenyl]-1*H*-tetrazole;

3-fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylme-thyloxy]ethyl]benzoic acid;

2-fluoro-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthyl-methyloxy]ethyl]benzoic acid;

3-methoxy-4-[2-[7-(2-quinolinylmethyloxy)-2-naphthyl-methyloxy]ethyl]benzoic acid;

3-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethyloxy]-ethyl]benzoic acid;

4-[2-[7-(2-quinolinylmethyloxy)-2-naphthylmethylthio]-ethyl]benzoic acid;

3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]ethyl]benzoic acid;

4-[1-methyl-2-[7-(2-quinolinylmethyloxy)-2-naphthylsul-fonylamino]ethyl]benzoic acid;

4-[1,1-dimethyl-2-[7-(2-quinolinylmethyloxy)-2-naphthyl-sulfonylamino]ethyl]benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylami-no]propyl]benzoic acid;

5-[4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonyl-amino]propyl]phenyl]-1*H*-tetrazole;

3-fluoro-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]propyl]benzoic acid;

3-methoxy-4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]-sulfonylamino]propyl]benzoic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic acid;

4-[2-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]propyl]phenylacetic acid;

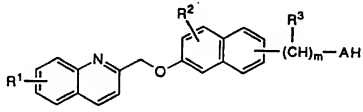
4-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic acid;

2-[1-[[7-(2-quinolinylmethyloxy)-2-naphthyl]sulfonylamino]ethyl]phenylacetic acid.

10. A process for the preparation of the compound of general formula I of claim 1, and the pharmaceutically acceptable salts thereof,

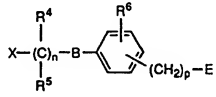
in which process:

a) when in formula I -A- is -O- or -S-, then a compound of general formula II,



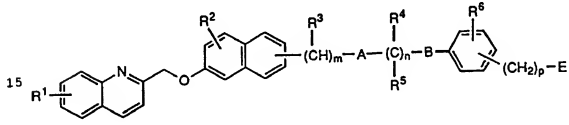
II

wherein R^1, R^2, R^3 and m have the above defined meanings and A is oxygen or sulfur, is reacted with a compound III,



III

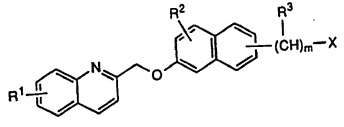
wherein R^4, R^5, R^6, B, n and p have the above defined meanings, X is a chlorine or bromine atom or an alkyl- or arylsulfonate group and E can be equivalent to the group D in I or, when D in formula I is COOH or a 5-tetrazolyl group, then E is CN, or alternatively, when D in formula I is COOH, then E can contain a suitable carboxy-protecting group; the reaction being carried out previously preparing a salt of the alcohol or thiol II, subjecting it to the action of a suitable base, then reacting it with the compound III, to obtain a compound of formula IV,



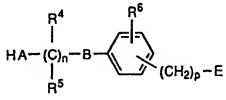
IV

which coincides with I or is converted into I either removing any COOH-protecting groups present in E or hydrolysing the nitrile group present in E to carboxylic acid or converting said nitrile group to a 5-tetrazolyl group by reaction with sodium azide;

b) alternatively, when in formula I -A- is -O- or -S-, then a compound of formula IV is obtained following the same process as above, starting from compounds V and VI,



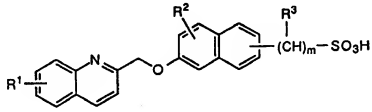
V



VI

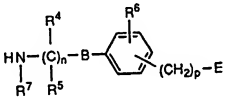
wherein R^1, R^2, R^3, R^4, R^5, R^6, B, X, n, m and p have the above defined meanings, A is oxygen or sulfur and E represents the groups defined above with the exception of the 5-tetrazolyl group;

c) when in formula I -A- is $-SO_2NR^7-$, then a compound of general formula VII,



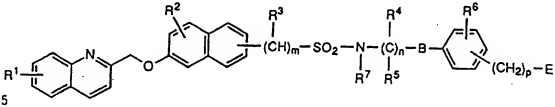
VII

wherein R^1, R^2, R^3 and m have the above defined meanings, is reacted with a compound VIII,



VIII

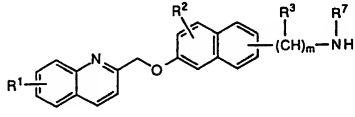
wherein R^4, R^5, R^6, R^7, B, E, n and p have the above defined meanings; the reaction being carried out previously preparing the acid chloride of the compound VII, then reacting it with compound VIII in the presence of a base, to obtain a compound of formula IXa,



IXa

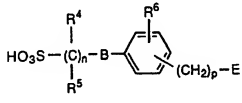
which coincides with I or is converted into I either removing any COOH-protecting groups present in E or hydrolysing the nitrile group present in E to carboxylic acid or converting said nitrile group to a 5-tetrazolyl group by reaction with sodium azide;

d) when in formula I -A- is $-NR^7SO_2-$, then a compound of general formula X,



X

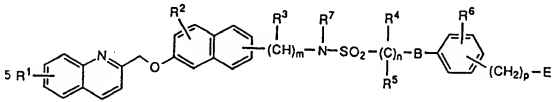
wherein R^1, R^2, R^3, R^7 and m have the above defined meanings, is reacted with a compound XI,



XI

wherein R^4, R^5, R^6, R^7, B, E, n and p have the above defined meanings; the reaction being carried out previously preparing the acid chloride of compound XI, then reacting it with compound X in the presence of a

base, to obtain a compound of formula IXb,



IXb

which coincides with I or is converted into I either removing any COOH-protecting groups present in E or hydrolysing the nitrile group present in E to carboxylic acid or converting said nitrile group to a 5-tetrazolyl group by reaction with sodium azide;

e) alternatively, when in formula I -A- is $-SO_2NR^7-$ or $-NR^7SO_2-$, then a compound of general formula IXa or IXb, wherein R^1, R^2, R^3, R^4, R^5, R^6, B, E, n, p and m have the above defined meanings and R^7 is a (C_1-C_4)-alkyl, can be obtained starting from a compound IXa or IXb where R^7 is hydrogen, by reaction with a (C_1-C_4)-alkyl chloride or bromide in the presence of a suitable base;

f) when compound I in the form of a salt is desired, it can be prepared starting from I, by treatment with a base or a suitable ion-exchanger, according to conventional methods.

11. The use of a compound of any one of claims 1 to 11 in the preparation of a medicament for the therapeutical treatment of leukotriene-mediated diseases.

12. The use according to claim 11, wherein the leukotriene-mediated diseases are of inflammatory or allergic type.

13. The use according to claim 12, wherein the inflammatory or allergic diseases are: bronchial asthma,

allergic rhinitis, allergic conjunctivitis, rheumatoid arthritis, osteoarthritis, tendinitis, bursitis or psoriasis.

14. The use according to claim 11, wherein the leukotriene-mediated diseases are of cardiovascular type.

15. The use according to claim 14, wherein the diseases of cardiovascular type are: cardiac ischemia, cardiac infarction, coronary spasm, cardiac anaphylaxis, cerebral oedema or endotoxic shock.

INTERNATIONAL SEARCH REPORT

Intern tal Application No
PC1/EP 96/05811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/14 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 96 04267 A (LABORATORIOS MENARINI S.A) 15 February 1996 cited in the application see the whole document ---	1,11
P,A	WO 96 04246 A (LABORATORIOS MENARINI S.A) 15 February 1996 see the whole document ---	1,11
A	WO 89 12628 A (RORER INTERNATIONAL INC.) 28 December 1989 see page 1 - page 5 & US 4 920 131 A cited in the application ---	1,11
A	WO 89 05294 A (LEO PHARMACEUTICAL PRODUCTS LTD.) 15 June 1989 see page 1 - page 3 --- -/--	1,11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 1997	21.05.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kyriakakou, G

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PC\/EP 96/05811

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89 04304 A (RORER INTERNATIONAL) 18 May 1989 see page 1 - page 4 ---	1,11
A	EP 0 315 399 A (RORER INTERNATIONAL INC.) 10 May 1989 cited in the application see the whole document -----	1,11

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/EP 96/05811

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9604267 A	15-02-96	AU 3253995 A	04-03-96
WO 9604246 A	15-02-96	AU 3221995 A	04-03-96
WO 8912628 A	28-12-89	US 4920131 A	24-04-90
		EP 0348155 A	27-12-89
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		AU 2611888 A	05-07-89
		CA 1336602 A	08-08-95
		DE 3851232 D	29-09-94
		DE 3851232 T	02-02-95
		DK 170576 B	30-10-95
		EP 0420844 A	10-04-91
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